The Relation of Glutathione to the Diabetogenic Effect of Adrenal Steroids

Arnold Lazarow, M.D., Ph.D.

DEPARTMENT OF ANATOMY, WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE, CLEVELAND

INTRODUCTION

In the past few years it has been shown that glutathione plays an important role as a protective agent in the pathogenesis of experimental diabetes.[1] In 1946 we reported that the injection of glutathione in doses equivalent to that present within the body completely protected rats against a diabetogenic dose of alloxan.[2] We further suggested at that time that glutathione could protect against human diabetes if similar diabetogenic agents appear within the human body.[2] Since the symptoms of diabetes may result from an endocrine imbalance between the pancreas on the one hand and the pituitary, adrenal cortex, etc. on the other, it was important to determine the relationship between glutathione and these endocrine glands.

As early as 1939 Gregory and Goss[3] noted that the injection of the pituitary growth hormone lowered the glutathione content of the tissues. More recently Conn and others[4] reported that the injection of certain preparations of purified corticotropin into man lowered the level of glutathione in the blood and there appeared to be a correlation between the diabetogenic potency of the corticotropin preparation and the fall in the blood glutathione. In one case of human diabetes induced by injection of corticotropin, glutathione administration was reported to produce a transitory decrease in glycosuria.[5] When cortisone became available in 1949 we began a study of the role of glutathione in experimental steroid diabetes; some results have been reported.[6,7]

Read before the Annual Meeting of the American Diabetes Association, Atlantic City, June 9, 1951.

METHODS

Normal and subdiabetic Sprague-Dawley rats were used. Subdiabetic animals were prepared by fasting rats (weighing approximately 100 gm.) for 48 hours and injecting alloxan in doses of 15 mg. per kg. Animals with a decreased glucose tolerance but normal blood sugar values (subdiabetes) were selected and allowed to reach a weight of 300 gm.

Rats weighing approximately 300 gm. were placed in metabolism cages and fed a high carbohydrate liquid diet* by stomach tube in the morning and early evening. Although some of the rats developed an initial glycosuria the normal rats became aglycosuric within a few weeks and the subdiabetic rats became aglycosuric within one month.

Aqueous suspensions of cortisone acetate (Merck) or compound F (hydrocortone acetate)† containing 1.5 per cent benzyl alcohol were injected subcutaneously in two divided doses prior to feeding. In a few experiments the cortisone was suspended in corn oil and injected subcutaneously. Corticotropin (Armour preparation No. 6061)‡ was dissolved in dilute hydrochloric acid and injected subcutaneously in five divided doses per day. The dose equivalents of corticotropin used were expressed in terms of the Armour standard ACTH preparation (1ALA). Specimens of urine were collected daily under toluene and the glucose excretion was determined by the carmelization method of Somogyi,[10] adapted to the Klett colorimeter. Solutions of 0.5 M glutathione, 0.5 M cysteine (free base), 0.5 M ascorbic acid, 0.5 M glutamic acid, or 1.0 M DL alanine, were adjusted to *p*H 7.4 and injected intraperitoneally in doses of 0.5 cc. per 100 gm. of body weight, ten minutes prior to each feeding. Determination of the blood sugar was made by the Folin-Malmros micro method.[11] Reduced glutathione§ was determined by a micro method which is based on the reaction of alloxan with glutathione.[12] Hematocrit readings were made by the Van Allen method.[13] The count of eosinophils was made by the method of Hills and others.[14]

*The high carbohydrate liquid diet of Reinecke and others,[8] as modified by Ingle,[9] was diluted with an additional 25 per cent water and administered in increasing amounts over a five-day period. After the fifth day, 32 cc. were fed each day and the total caloric intake remained the same.[9] This dilution of the diet facilitates the passage of the food through a No. 8 French catheter.

†Supplied by Dr. August Gibson of Merck and Company.

‡Supplied by Dr. I. M. Bunding of Armour and Company.

§Unless otherwise specified, glutathione will imply the reduced form of this compound.

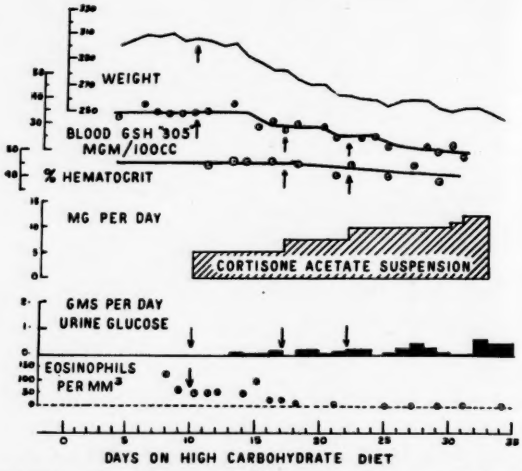


FIGURE 1 The effect of graded doses of cortisone on the blood glutathione (GSH) level of the normal rat (rat 1)

RESULTS

The Effect of Adrenal Steroids on the Blood Glutathione Level

In general, the injection of steroids produced a drop in the blood glutathione level. Since all the glutathione of the blood is contained within the blood cells,[15] hemodilution would produce a corresponding decrease in the blood glutathione level. Although steroid injection also produces a drop in the blood hematocrit, the fall in blood glutathione is much greater than the corresponding change in the hematocrit reading and therefore is highly significant.

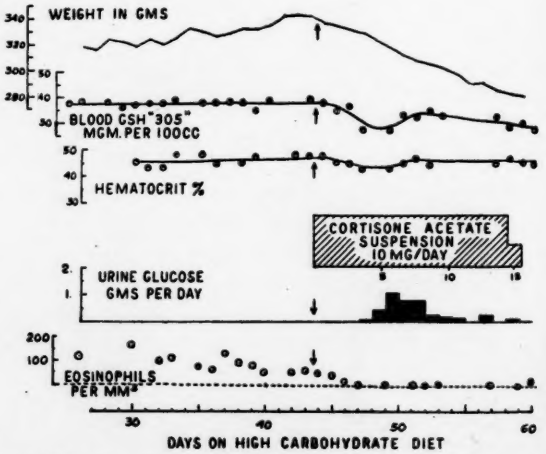


FIGURE 2 The effect of large doses of cortisone on the blood glutathione (GSH) level: mild diabetes (rat 2)

When varying doses of aqueous suspension of cortisone acetate were injected into normal rats (Figure 1) there was a decrease in blood glutathione level which paralleled fairly closely the increasing cortisone doses. When cortisone was injected in a constant dose of 10 mg. per day, some rats developed a transitory glycosuria (Figure 2). The sugar appeared in the urine on the fifth day, reached a maximum on the sixth day and disappeared by the tenth day. In this animal the drop in glutathione level seemed to parallel the glycosuria, for the glutathione returned toward normal when the glycosuria disappeared. Although there was some decrease in blood hematocrit (maximum 10 per cent), the maximum drop in glutathione (30 per cent) was much greater than the hematocrit drop.

Other animals developed a severe glycosuria on a cortisone dose of 10 mg. per day. Figure 3 shows observations on a rat which excreted a maximum of 5.6 gm. of sugar on the sixth day. The glycosuria stabilized at 2 to 3 gm. per day between the eighth and tenth days. Correspondingly, there was a much greater drop in blood glutathione level (50 per cent) and it remained low for the entire period. The hematocrit reading dropped only 15 per cent. However, a drop in the glutathione level can occur in the absence of significant glycosuria. This

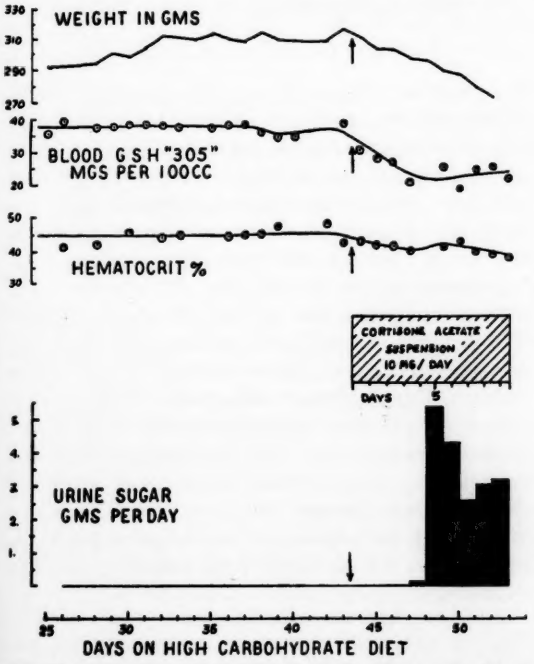


FIGURE 3 The effect of large doses of cortisone on the blood glutathione (GSH) level: severe diabetes (rat 7)

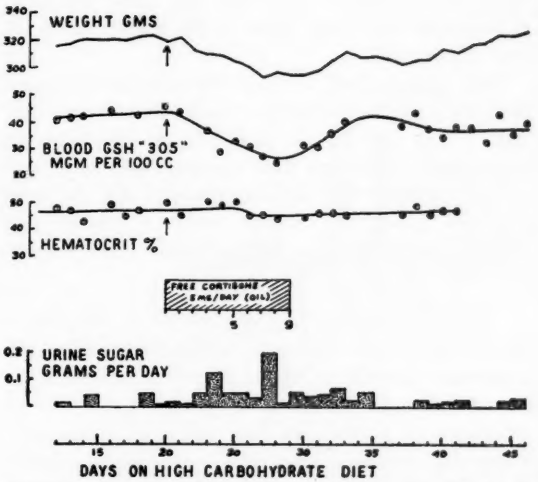


FIGURE 4 The effect of small doses of cortisone on the blood glutathione (GSH) level in the absence of glycosuria (rat 17) (Note: The scale for the urine sugar in this figure is ten times greater than in other figures)

is illustrated in Figure 4. In this case the free alcohol of cortisone was injected as an oily suspension in doses of 5 mg. per day. Although the glycosuria induced was insignificant (less than 0.2 gm. per day), there was a 40 per cent drop in the blood glutathione level.

Hydrocortone acetate (compound F) likewise induced a drop in the blood glutathione level. When 5 mg. of compound F were administered per day (see Figure 5), there was a marked drop in glutathione level, although there was no significant glycosuria. Larger doses of

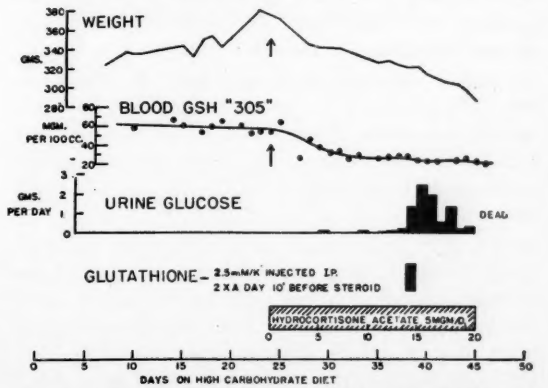


FIGURE 5 The diabetogenic effect of glutathione (GSH) in a rat treated with compound F (rat 225) (Note: The blood samples for glutathione determinations were drawn once a day prior to the glutathione injection. Although glutathione injections cause a transitory rise in blood level, the value had returned to normal long before the next glutathione determination on the following day)

hydrocortone (10 to 12.5 mg. per day) produced glycosuria as well as a drop in the glutathione level (not illustrated).

These studies clearly indicate that injection of steroid produces a fall in the blood glutathione level which is greater than can be accounted for on the basis of hemodilution. Although there appears to be some relationship between the induced glycosuria and the drop in blood glutathione, smaller doses of steroid may induce a large decrease in glutathione level without any significant glycosuria.

The Production of Steroid Diabetes in the Rat

It has been found necessary to use larger doses of steroid to produce diabetes in the rat than was previously reported by Ingle.[16] In our hands 5 mg. of cortisone or hydrocortone acetate per day given as an aqueous suspension produced insignificant glycosuria (Figures 1, 4, 5); whereas 10 mg. per day of these compounds produced glycosuria in all cases. In the experiments carried out by Ingle the steroids were obtained by biological isolation and they were administered as a suspension of the free alcohol in oil. In the studies here reported, the injection of 5 mg. per day of cortisone (free alcohol) and 5.6 mg. of cortisone acetate in oily suspensions did not produce significant glycosuria. Since the same diet and same strain of rats were used, the cause of the decreased effectiveness of the synthetic steroid is not clear.

Transitory Nature of Steroid Diabetes

Following administration of steroids glycosuria seldom appeared until the fourth or fifth day. The maximum glycosuria was usually observed on the sixth or seventh day and thereafter it tended to decrease even though the steroid injections were maintained at a constant dose. The glycosuria disappeared completely in some animals; in others it reached a fairly constant level and persisted throughout the period of steroid administration. In animals in which the glycosuria had disappeared it could be reestablished by increasing the steroid dose. Withdrawal of the hormone abolished the glycosuria. It is of interest that in the case of the animals injected with cortisone the eosinophil count did not reach its minimum value until the third or fourth day of steroid administration (see Figure 2). This would suggest that the cortisone may be absorbed slowly, following this mode of administration.

Abnormalities in glucose tolerance, induced by steroid administration, paralleled the glycosuria. For example, in a rat receiving 10 mg. of cortisone per day (Figure 6) the glucose tolerance was abnormal on the sixth day

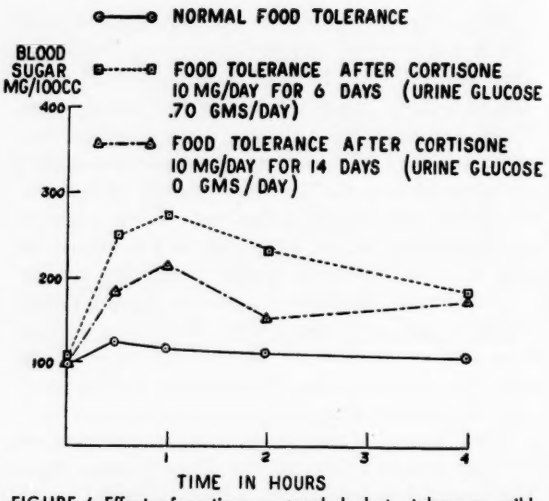


FIGURE 6 Effect of cortisone on carbohydrate tolerance: mild diabetes (rat 2 force-fed a high carbohydrate diet at zero time)

of cortisone administration, when the glycosuria was 0.7 gm. By the fourteenth day, the glycosuria had disappeared and the carbohydrate tolerance had likewise improved. In the case of another rat treated with cortisone in which the glycosuria was 3.5 gm. per day, the carbohydrate tolerance was markedly decreased (Figure 7).

Effect of Injected Glutathione on Steroid Diabetes

The injection of glutathione into rats with severe cortisone-diabetes produced death; in animals with moderate cortisone-diabetes, equivalent doses of glutathione intensified the diabetes. Rat No. 13 (not illustrated) received 10 mg. of cortisone per day. Glycosuria appeared on the fourth day; a maximum of 3 gm. of sugar was excreted on the sixth day; from the seventh to the eleventh day, the glycosuria had stabilized at about 2 gm. per day. When a single dose of glutathione (2.5 mM per kg.) was injected on the eleventh day the rat died within two hours of the injection. This experiment was repeated in three other animals with severe cortisone diabetes with similar results. Over four times this dose of glutathione has been given to normal animals without ill effects. When glutathione was injected into a cortisone-diabetic rat in which the daily sugar excretion ranged between 0.3 and 0.4 gm. the glycosuria* was markedly increased

*Glutathione does not carmelize with sodium carbonate. Therefore, even though some of the injected glutathione may be excreted in the urine it would not interfere with the determination of urine glucose by the Somogyi method.

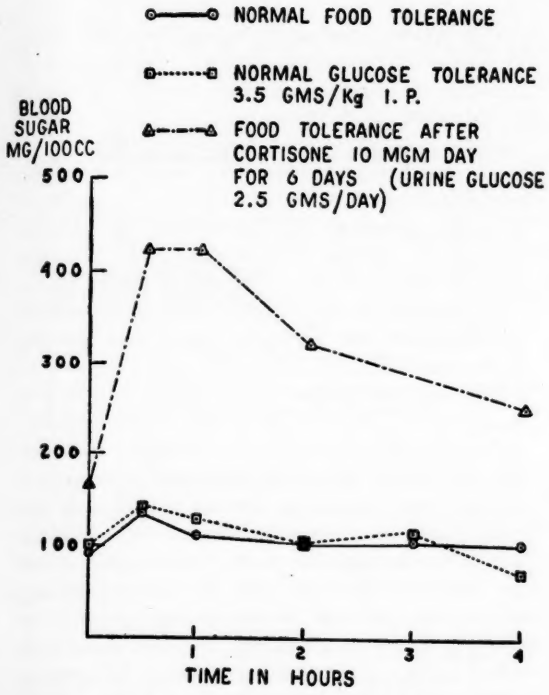


FIGURE 7 Effect of cortisone on carbohydrate tolerance: severe diabetes (rat 7 force-fed a high carbohydrate diet at zero time)

(Figure 8). The glutathione was injected twice a day, ten minutes before each feeding (in doses totaling 5.0 mM per kg. per day) on the eleventh, fourteenth and twenty-second days of cortisone administration. In some cases there was a tenfold increase in the glycosuria during the 24 hours following glutathione injection.

Figure 9 illustrates a similar experiment carried out on a subdiabetic animal which had been given a subthreshold dose of alloxan four months prior to the cortisone administration. Although this rat had an abnormal glucose tolerance, the glucose excreted on the high carbohydrate diet was insignificant. The injection of only 4 mg. per day of cortisone acetate produced glycosuria in this animal. A maximum of 1 gm. of sugar was excreted on the sixth day, and thereafter the glycosuria ranged from 0.5 to 0.8 gm. per day. Less cortisone was required to induce glycosuria in a subdiabetic animal than was the case in normal animals. Glutathione was administered in doses of 5.0 mM per kg. per day on five different occasions over the 67-day period of steroid administration. In every instance there was a

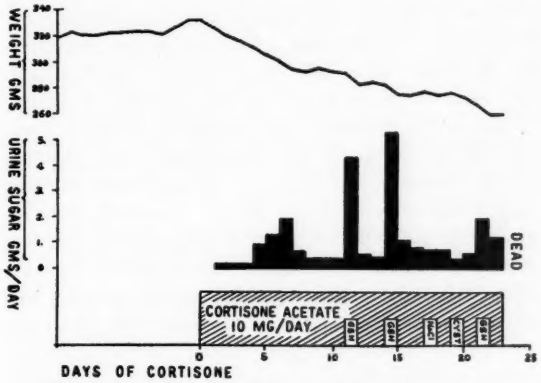


FIGURE 8 The diabetogenic effect of glutathione (GSH) in a cortisone-treated animal (rat 18)

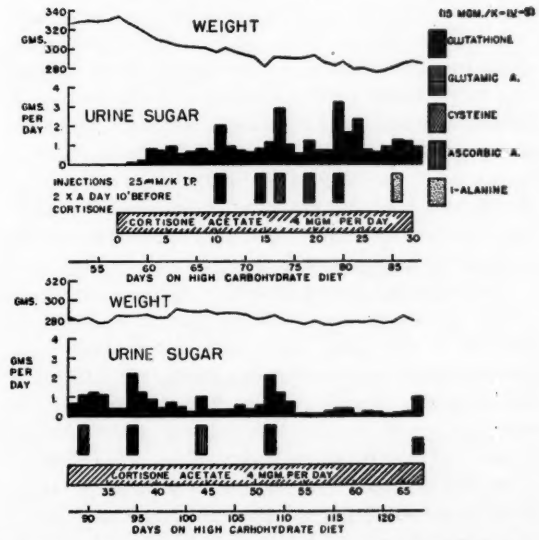


FIGURE 9 The diabetogenic effect of glutathione (GSH) in a rat given one subthreshold dose of alloxan and later treated with small doses of cortisone (rat G)

several-fold increase in glycosuria† during the 24 hour period following glutathione injection. Within one or two days the glycosuria had returned to its preinjection level. Cysteine was injected in equivalent doses on two occasions and it produced a marked effect on the sixteenth day and a lesser effect on the thirty-second day. Ascorbic acid injection produced a slight increase in glycosuria; glutamic acid and alanine injection produced insignificant effects.

†See immediately previous footnote.

When diabetes is produced by the administration of compound F, glutathione injection likewise increases the glycosuria. In rat No. 229 (not illustrated) which had been receiving 10 to 12 mg. per day of hydrocortisone, the glycosuria had declined to 0.66 gm. per day by the thirteenth day. Glutathione was injected on the fourteenth day and 5 gm. of sugar were excreted in the following 24 hours. By the eighteenth day the glycosuria had returned to its previous level. The experiment illustrated in Figure 5 is of special interest. This rat had been receiving 5 mg. of compound F per day and insignificant amounts of sugar (less than 0.15 gm. per day) were excreted. On the fourteenth day of steroid administration, glutathione injection induced a marked glycosuria which amounted to 1.4 gm. per day. The increased glycosuria persisted for several days after the glutathione injection. It would appear that glutathione exerted a prolonged effect in this animal.

Similar results had been obtained with diabetes induced by administration of corticotropin. A rat (Figure 10) injected with a dose equivalent to 20 mg. per day of Armour Standard (1ALA) showed maximum glycosuria of 0.5 gm. on the third day and slight glycosuria (0.1 to 0.3 gm.) thereafter. On the thirteenth day, glutathione was also injected and the excretion of sugar rose to 1.3 gm. Within three days the glycosuria had returned to its preinjection level.

The increased glycosuria which results from glutathione administration is due in part, at least, to an increase in the blood sugar level. Serial blood sugar determinations were carried out during the four hours following the morning stomach intubation on the mornings preceding and following the glutathione injection. It was found that glutathione, when injected prior to the forced feeding, not only induced higher blood sugar levels, but it caused the blood sugar levels to remain elevated for longer periods. The elevation in the blood sugar was greatest in those animals showing the greatest glycosuria. Although glutathione will reduce ferricyanide and therefore its injection will produce some apparent rise in the blood sugar value, as measured by the Folin-Malmros method, the observed blood sugar elevation cannot be explained on the basis of the reducing capacity of glutathione.* Figure 11 illustrates the most severe example of hyperglycemia which we

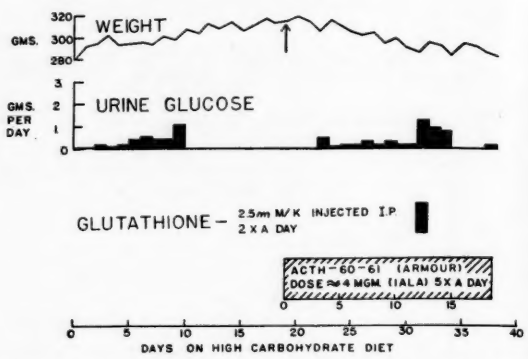


FIGURE 10 The diabetogenic effect of glutathione (GSH) in a rat treated with corticotropin (rat 36)

observed. Rat G (previously illustrated in Figure 9) had been receiving 4 mg. per day of cortisone. On the sixty-sixth day of steroid administration serial blood sugar determinations were made. The maximum blood sugar observed one hour after the morning feeding was 360 mg. per 100 cc. On the sixty-seventh day when glutathione was injected, the blood sugar level reached 1,428 mg. per 100 cc. Although the rat died between the second and third hours, the glucose excreted during this three-hour period was more than two and one-half times that observed during the previous 24 hours. It is not unlikely that the induced hyperglycemia may have caused death in this animal, for it should be recalled that similar doses of glutathione will uniformly kill rats with severe cortisone diabetes, i.e., if the preinjection glycosuria is 2 to 3 gm. per day.

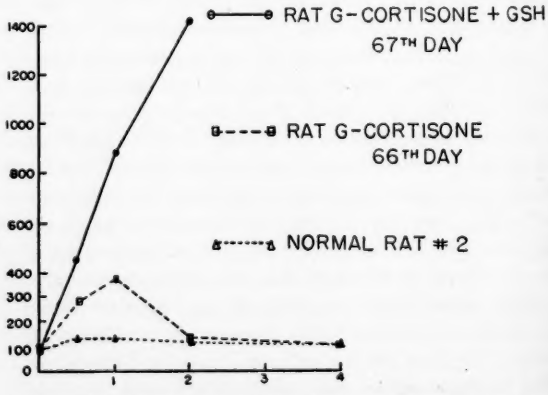


FIGURE 11 The blood sugar level of a cortisone-diabetic rat following glutathione (GSH) injection. Morning feeding was administered by stomach tube at zero time (same rat as in Figure 8)

*When equivalent doses of glutathione were injected into starved normal rats and serial blood sugar determinations were carried out, the maximum elevation in the apparent blood sugar level was less than 20 mg. per 100 cc. Thus within thirty minutes of its injection, much of the glutathione is destroyed or taken up by the tissues.

Effect of Glutathione in Normal Rats

When control animals given the high carbohydrate diet by forced feeding for long periods were injected with glutathione they showed an insignificant glycosuria. However, during the early period of adaptation to the high carbohydrate diet normal rats will show moderate glycosuria following injection of glutathione. Seven normal rats were injected at various time intervals after forced feeding (Figure 12). On the nineteenth day of feeding the high carbohydrate diet the average glycosuria induced by glutathione injection was 0.66 gm. Subsequent injections of glutathione produced progressively less glycosuria and on the sixty-third day, the glycosuria was insignificant. This decreased effectiveness of glutathione on subsequent injections is due to an adaptation to the diet and not due to an adaptation to glutathione, because rats given their first glutathione injection on the fiftieth day of the diet had insignificant glycosuria. Figure 12 further indicates that in the normal rat, cysteine and ascorbic acid produced some glycosuria, but had less effect than glutathione.

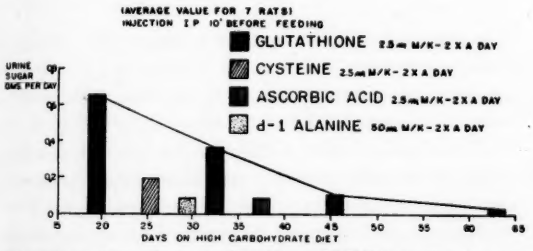


FIGURE 12 The effect of glutathione (GSH) injection in normal rats force-fed a high carbohydrate diet (Note: The scale for the urine sugar in this figure is ten times greater than in the other figures)

Effect of Glutathione in Alloxan-Diabetic Rats

Equivalent doses of glutathione were injected into rats with severe alloxan diabetes. There rats were fed freely a diet of a proprietary dog food.† The existing glycosuria was not increased by the glutathione injection, nor was the glutathione toxic. Glutathione injection likewise did not induce glycosuria in subdiabetic rats, i.e., alloxan-injected animals that had abnormal glucose tolerance.

Effect of Glutathione on Insulin Tolerance

Since glutathione is capable of inactivating insulin in vitro[17] glutathione was injected intraperitoneally (2.5 mM per kg.) simultaneously with varying test doses of regular insulin (2.5 to 20 units per kg. subcutaneously). Determinations of the blood sugar were made one-half, one, two, and four hours after injection. Although some inactivation of insulin might be expected in vivo, we found that glutathione injection modified only slightly the effect of insulin in lowering the blood sugar.

Effect of Glutathione on Eosinophil Count

The effect of glutathione (2.5 mM per kg.) given by intraperitoneal injection on the eosinophil count of normal animals is shown in Figure 13. There was no significant change until the fourth hour; there was then a 32 per cent decrease in eosinophils; by the eighth hour the count was decreased by only 17 per cent. The drop in eosinophil count which follows the injection of glutathione appears much later and is of much smaller magnitude than that which follows the injection of epinephrine.

DISCUSSION

Mechanisms by Which Adrenal Steroids Lower the Reduced Blood Glutathione Level

Both cortisone and hydrocortisone (compounds E and F) produce a significant drop in the level of blood glutathione. This decrease is much greater than can

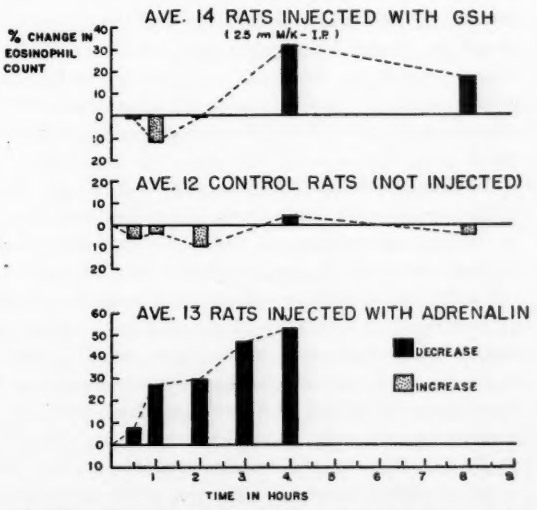


FIGURE 13 The effect of glutathione (GSH) injection on the eosinophil count of normal rats

†"Friskies"—Albers Milling Co.

be accounted for by changes in the blood hematocrit reading.

Some of the metabolic effects of adrenal steroids are illustrated in Figure 14. Adrenal steroids are known to produce lysis of lymphoid tissue.[18] Consequently, part of the increased nitrogen excretion[19] (which arises from protein breakdown) and part of the increased uric acid excretion[20] (which presumably arises from nucleic acid breakdown) have their origin in tissue destruction.

Although little is known about the metabolism of the pyrimidine portion of the nucleic acid molecule, increased amounts of this component should likewise be metabolized when cells are broken down under the influence of adrenal steroids. Figure 15 illustrates the scheme of metabolism of a pyrimidine (uracil), as postulated by Cerecedo.[21] These studies, which were done prior to the availability of radioisotopes, were carried out by feeding the proposed intermediate and determining the resulting increase in urinary nitrogen and urea. Although Cerecedo had postulated that alloxan was a normal intermediate in the metabolism of uracil, he later[22] excluded this compound as an intermediate because alloxan did not induce an increased excretion of urea as did the other intermediates. We know now that alloxan is an extremely reactive compound; its half life at *p*H 7.4 and 37° C. is about one minute.[23] Alloxan is rapidly converted to alloxanic acid. Therefore, it is possible that very little of the fed alloxan entered the metabolic pool as such, since most of the alloxan would be destroyed in the intestinal tract prior to its absorption. Alloxan may well be a normal intermediate in pyrimidine metabolism and this possibility should be further investigated using the more modern isotope techniques. Since uric acid can be oxidized to alloxan in vitro,[24] similar conversions might conceivably take place within the body under physiological conditions.

Previous work in this laboratory has shown that alloxan reacts with glutathione in at least two ways: it oxidizes glutathione to a disulfide derivative, and it reacts with glutathione to form a new compound[25] (probably an addition product). This latter compound is identified by means of its characteristic ultraviolet absorption spectrum maximum at 305 mμ. If alloxan-like compounds were formed in increased amounts as a consequence of steroid administration, these could react with glutathione as mentioned above and thereby produce a drop in the reduced glutathione level. It is also possible that the administration of adrenal steroids might alter the oxidation-reduction potential within the cell and thereby favor the oxidation of glutathione

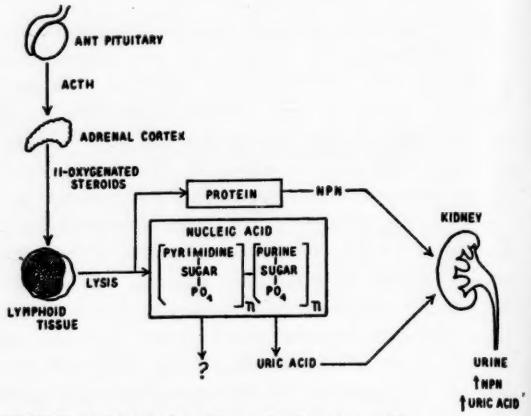


FIGURE 14 Metabolic effects of adrenal steroids

to its disulfide derivative. This could likewise produce a decrease in the reduced glutathione level in blood.

The Mechanism by Which Adrenal Steroids Induce Diabetes

This mechanism is not completely understood. Although these compounds promote the formation of liver glycogen, they decrease the utilization of carbohydrate as well.[16, 19] Since the induction of steroid diabetes in the rat is associated with a drop in the blood glutathione level, one wonders whether the diabetogenic mechanism and the mechanism concerned with lowering the blood glutathione are interrelated. Does the biochemical change which produces a drop in the blood glutathione also produce a decreased glucose utilization; or does the diabetes result from the liberation of diabetogenic intermediates?

The altered metabolic state resulting from the administration of adrenal steroids might favor the conversion of potential diabetogenic compounds into active ones. Although alloxan[26] and the oxidized form of

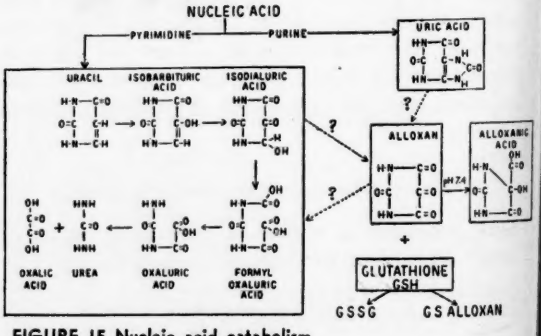


FIGURE 15 Nucleic acid catabolism

vitamin C, i.e. dehydroascorbic acid,[27] are capable of producing diabetes in experimental animals, both of these compounds can be reduced to nondiabetogenic derivatives, i.e. dialuric acid,[28] and ascorbic acid,[29] respectively. Dialuric acid is more stable than is alloxan and small amounts of dialuric acid may persist in tissue for considerable periods following alloxan injection.[30] A metabolic product of alloxan, i.e. alloxanic acid, has been reported as a normal constituent of urine.[31] Ascorbic acid is almost universally distributed within cells.[32] If the decreased reduced glutathione level of the blood which follows cortisone administration is a result of an altered oxidation-reduction potential within the cell, then this alteration would also favor the oxidation of nondiabetogenic compounds (i.e. ascorbic acid, dialuric acid or possibly other compounds) to their diabetogenic derivatives (see Figure 16).

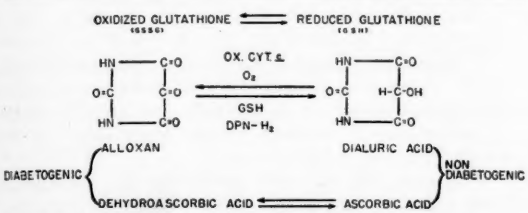


FIGURE 16 Origin of potential diabetogenic compounds

Although the diabetogenic effects of adrenal steroids disappear following the cessation of hormone injection, this does not necessarily rule out the possibility that the diabetic symptoms could result from the physiological liberation of diabetogenic agents. For, although alloxan and dehydroascorbic acid are capable of producing permanent diabetes, small doses of these compounds will produce a transitory diabetes. Furthermore, under certain conditions both alloxan[33] and dehydroascorbic acid[34] are capable of producing hyperglycemia without obvious morphological damage to the insulin-producing cells. Obviously, further work is indicated.

Diabetogenic Action of Glutathione

The finding that glutathione injection markedly potentiates steroid diabetes in experimental animals is in direct contrast to the study reported by Conn and others.[5] In a case of human diabetes induced by ACTH, glutathione injection was reported to decrease the glycosuria and the blood sugar level. To date we have injected glutathione into many animals receiving cortisone, hydrocortisone and ACTH, and we have almost invariably observed an increased glycosuria.

The mechanism by which glutathione potentiates the diabetes is not understood. Although glutathione is capable of inactivating insulin in vitro,[17] there are three observations which suggest that the diabetogenic effect of glutathione in vivo cannot be explained by this mechanism: (1) It was noted (Figure 12) that in the normal rat force-fed a high carbohydrate diet, glutathione was more effective in inducing glycosuria than was cysteine. By contrast cysteine is at least twice as effective in inactivating insulin in vitro as is glutathione.[17] (2) Whereas glutathione induced a very marked increase in glycosuria in steroid-treated rats (up to 5 gm. per day), it induced only mild glycosuria in the normal animal fed the high carbohydrate diet (0.66 gm. per day), and it did not increase the glycosuria in the alloxan-diabetic rat. Since rats with steroid diabetes are highly resistant to insulin,[16] it seems unlikely that insulin inactivation would induce the most marked glycosuria in steroid-injected animals. (3) Glutathione injection does not reduce the in vivo hypoglycemic effect of insulin significantly.

The possibility that glutathione injection liberates epinephrine and thereby increases the diabetic state has been considered and has not been completely ruled out. The 30 per cent drop in eosinophil count observed four hours after the glutathione injection is much less than that observed following epinephrine injection. If the increased glycosuria were due to epinephrine release (due to the stress of the intraperitoneal injection) glutathione would be equally effective in alloxan-diabetic rats. Similarly, the injection of a number of closely related compounds should be equally effective in producing stress, and this does not appear to be the case.

Since cortisone injection results in an increased ketosteroid excretion,[35] part of the injected steroid is destroyed by oxidation of the side chain. Reducing agents, such as glutathione, could conceivably protect adrenal steroids from destruction within the body and thereby prolong their diabetogenic effects.

It is not improbable that glutathione might produce its diabetogenic effect in the animals injected with cortisone by acting on one of the enzymes involved in carbohydrate metabolism. Although the activity of many enzymes is dependent upon the presence of active sulfhydryl groups,[36, 37] it is difficult to explain the diabetogenic action of injected glutathione in terms of the known effects of glutathione on sulfhydryl enzymes.*

*A possible explanation is given in my discussion of Dr. Anderson's question.

In some ways the effect of glutathione in potentiating glycosuria simulates the effect of growth hormone. Engle has recently reported that growth hormone will induce clinical diabetes in rats that were maintained on a subdiabetogenic dose of corticotropin.[38] We have found (Figure 5) that glutathione injection had a similar effect in rats receiving small doses of compound F. The possibility that glutathione may have other metabolic activities similar to growth hormone needs further investigation.

Thus we see that glutathione is a two-edged sword, for although it markedly potentiates steroid diabetes in the rat, glutathione injection nevertheless protects against chemical diabetes induced by alloxan[2] or dehydroascorbic acid.[29] The protective effect may be attributed to the removal of potential diabetogenic compounds in the blood and in the beta cells, etc.; whereas the potentiating effect probably results from a direct action of glutathione on some enzyme system in a peripheral tissue such as the liver. Further studies are needed to determine the significance of these reactions.

SUMMARY

Cortisone and compound F, when injected into normal rats given a high carbohydrate diet by forced feeding, induced a drop in the level of reduced glutathione in the blood. Small doses of these steroids lowered the reduced glutathione levels without producing any significant glycosuria. Larger doses induced glycosuria as well.

Glutathione injection increased the glycosuria and hyperglycemia in rats with steroid diabetes (induced by cortisone, compound F, or ACTH). In animals receiving small doses of compound F, glutathione injection induced glycosuria.

By contrast, glutathione induced only mild glycosuria in normal animals during the early period of adaptation to a high carbohydrate diet (given by forced feeding) and it produced insignificant effects in alloxan-diabetic rats.

The mechanism of the diabetogenic action of glutathione and the mechanism by which steroid injection lowers the reduced blood glutathione have been discussed.

This investigation was supported by a research grant, No. A20C, from the National Institutes of Health, U. S. Public Health Service.

REFERENCES

[1] Lazarow, A.: Factors controlling the development and progression of diabetes. Physiol. Rev. *29*:48-74, 1949.

[2] Lazarow, A.: Protective effect of glutathione and cysteine against alloxan diabetes in the rat. Proc. Soc. Exper. Biol. & Med. *61*:441-47, 1946.

[3] Gregory, P. W., and Goss, H.: Glutathione values of livers and muscles of rabbits after injection of growth hormone. Growth *3*:159-64, 1939.

[4] Conn, J. W., Louis, L. H., and Johnston, M. W.: Metabolism of uric acid, glutathione, and nitrogen and excretion of "11-oxysteroids" and 17-ketosteroids during induction of diabetes in man with pituitary adrenocorticotropic hormone. J. Lab. & Clin. Med. *34*:255-69, 1949.

[5] Conn, J. W., Louis, L. H., and Johnston, M. W.: Alleviation of experimental diabetes in man by administration of reduced glutathione (GSH): Metabolic implications. Science *109*:279-80, 1949.

[6] Lazarow, A., and Berman, J.: The production of diabetes in rats with cortisone and its relation to glutathione. Anat. Rec. *106*:215, 1950.

[7] Lazarow, A.: Glutathione potentiation of cortisone-induced glycosuria in the rat. Proc. Soc. Exper. Biol. & Med. *74*:702-05, 1950.

[8] Reinecke, R. M., Ball, H. A., and Samuels, L. T.: High fat and high carbohydrate diets that can be fed to rats by stomach tube. Proc. Soc. Exper. Biol. & Med. *41*:44-46, 1939.

[9] Ingle, D. J., Sheppard, R., Oberle, E. A., and Kuizenga, M. H.: Comparison of acute effects of corticosterone and 17-hydroxycorticosterone on body weight and urinary excretion of sodium chloride, potassium, nitrogen and glucose in normal rat. Endocrinology *39*:52-57, 1946.

[10] Somogyi, M.: A rapid method for the estimation of urine sugars. J. Lab. & Clin. Med. *26*:1220-23, 1940-41.

[11] Folin, O., and Malmros, H.: An improved form of Folin's micro method for blood sugar determinations. J. Biol. Chem. *83*:115-20, 1929.

[12] Lazarow, A., Patterson, J. W., and Cooperstein, S.: (To be published.)

[13] Van Allen, C. M.: Hematocrit method. J. Lab. & Clin. Med. *10*:1027-40, 1924-25.

[14] Hills, A. G., Forsham, P. H., and Finch, C. A.: Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone (ACTH) in man. Blood *3*:755-68, 1948.

[15] Litarczek, G., and Dinischiouti, G. T.: On the penetration of glutathione in the interior of the erythrocyte. Compt. rend. Soc. de biol. *114*:285-87, 1933.

[16] Ingle, D. J.: The production of experimental glycosuria in the rat. Recent Progress in Hormone Research *2*:229-53, 1948.

[17] du Vigneaud, V., Fitch, A., Pekarek, E., and Lockwood, W. W.: The inactivation of crystalline insulin by cysteine and glutathione. J. Biol. Chem. *94*:233-42, 1931-32.

[18] Dougherty, T. F., and White, A.: Effect of pituitary adrenotropic hormone on lymphoid tissue. Proc. Soc. Exper. Biol. & Med. *53*:132-33, 1943.

[19] Sayers, G.: The adrenal cortex and homeostasis. Physiol. Rev. *30*:241-320, 1950.

[20] Forsham, P. H., Thorn, G. W., Bergner, G. E., and Emerson, K., Jr.: Metabolic changes induced by synthetic 11-dehydrocorticosterone acetate, including comparative studies with synthetic desoxycorticosterone and lipo-adrenal cortex. Am. J. Med. *1*:104-34, 1946.

[21] Cerecedo, L. R.: Studies on the physiology of pyrimidines. IV. Further experiments on the intermediary metabolism of uracil. J. Biol. Chem. *93*:269-74, 1931.

[22] Cerecedo, L. R.: Studies on the physiology of pyrimidines. VI. The fate of parabanic acid, alloxan, and alloxantin in the organism of the dog. J. Biol. Chem. *93*:283-91, 1931.

[23] Patterson, J. W., Lazarow, A., and Levey, S.: Alloxan and dialuric acid—their stabilities and ultra violet absorption spectra. J. Biol. Chem. *177*:187-95, 1949.

[24] Gilman, H.: Organic Chemistry, John Wiley & Sons, New York, 1938.

[25] Patterson, J. W., Lazarow, A., and Levey, S.: Reactions of alloxan and dialuric acid with the sulfhydryl group. J. Biol. Chem. *177*:197-204, 1949.

[26] Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B.: Necrosis of islets of Langerhans produced experimentally. Lancet *1*:484-87, 1943.

[27] Patterson, J. W.: The diabetogenic effect of dehydroascorbic and dehydroisoascorbic acids. J. Biol. Chem. *183*:81-88, 1950.

[28] Lazarow, A., Patterson, J. W., and Levey, S.: The mechanism of cysteine and glutathione protection against alloxan diabetes. Science *108*:308-09, 1948.

[29] Patterson, J. W., and Lazarow, A.: Sulfhydryl protection against dehydroascorbic acid diabetes. J. Biol. Chem. *186*:141-44, 1950.

[30] Siliprandi, N.: *In vivo* and *in vitro* determination of alloxan in blood and tissues. Arch. di sc. biol. *33*:431-44, 1949.

[33] Seligson, D., Seligson, H., Shapiro, B., Paley, R. G., Riaboff, T., and Lukens, F.D.W.: Attempts to demonstrate alloxan in human urine. Federation Proc. *10*:124, 1951.

[32] Mitchell, P. H.: A Textbook of Biochemistry, McGraw Hill, New York, 1946.

[33] Molander, D. W., and Kirschbaum, A.: Altered glucose tolerance with histologically normal islets following repeated small doses of alloxan. Endocrinology *44*:391-99, 1949.

[34] Patterson, J. W., and Lazarow, A.: (To be published.)

[35] Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The physiologic effects of cortisone and adrenocorticotropic hormone in man. Arch. Int. Med. *85*:199-258, 1950.

[36] Barron, E. S. G., and Singer, T. P.: Studies on biological oxidations. XIX. Sulphydryl enzymes in carbohydrate metabolism. J. Biol. chem. *157*:211-40, 1945.

[37] Singer, T. P., and Barron, E. S. G.: Studies on Biological oxidations. XX. Sulphydryl enzymes in fat and protein metabolism. J. Biol. Chem. *157*:241-53, 1945.

[38] Engle, F. L., Coggins, W. J., Lynn, W., and Viau, A.: Growth hormone induced diabetes in the rat. Federation Proc. *10*:39, 1951.

DISCUSSION

DR. DWIGHT J. INGLE *(Kalamazoo, Mich.):* I congratulate Dr. Lazarow on this and other studies which he has carried out on experimental diabetes. His results showing the diabetogenic activity of cortisone are qualitatively like our own. We are using cortisone acetate in suspension to induce diabetes in normal rats. The fluid diet which we force-feed has about 8 gm. of available carbohydrate per day. Ten mg. per day of cortisone acetate causes an average excretion of 4 to 6 gm. of glucose per rat per day, which is somewhat more severe than that Dr. Lazarow has found.

I should like to be able to offer some further intelligent suggestion as to what the mechanism may be for the diabetogenic activity of glutathione, but I have none. I do want to make one additional comment. In our studies on the effect of hormones upon experimental diabetes, studies which I summarized before this Association a few years ago, we found that most hormones will affect the severity of diabetes. Most of them will exacerbate diabetes under one experimental condition or another.

We became interested in the possibility that if one were to screen compounds for effects upon experimental diabetes, we might find a large number of substances which would either exacerbate it or decrease the severity. We set up such a program in my laboratory. We had 40 metabolism cases set up for this study, and we began very enthusiastically to take this and that compound off the shelf and try it out. The long and short of it is that we very quickly found several compounds which affected the severity of diabetes in our animals.

My curiosity overcame me. I abandoned, temporarily, at least, the program of screening compounds. We have spent our time on more penetrating studies of a few specific substances which affect the severity of diabetes in the rat.

I think we have an adequate basis for the prediction that if one were to do an extensive screening study, we would find that many substances now unrecognized will affect diabetes, at least in the experimental animal.

DR. GEORGE ANDERSON *(Brooklyn, N. Y.):* Dr. Lazarow's finding of an apparently antithetical relationship between the presence of available sulfhydryls and the production of (rather than the expected sulfhydryl protection from) experimental diabetes by cortisone is,

I believe, not too difficult of reasonable explanation. It has been thought by some workers in this field that sulfhydryl deficiency causes failure of the beta cells via failure of their intrinsic intracellular enzyme mechanisms which are extremely sensitive to sulfhydryl depletion. This, I think, is well borne out by the potentiating effect of dehydroascorbic acid as well as dietary depletion of available sulfhydryls in the promotion of alloxan diabetes and also by the protection from alloxan diabetes afforded the beta cells by sulfhydryls.

It must be remembered, however, that the same sulfhydryl deficiency which is created by cortisone would simultaneously impair the function not only of the beta cells but remotely of all of those peripheral carbohydrate enzyme-systems which are known to be sulfhydryl obligates or to depend on sulfhydryls for their functional integrity. Notable among these mechanisms are the mutases and those enzyme and coenzyme systems required for phosphorylative glycogenolysis, and possibly some of the phosphatases (although not the glucose-6-phosphatase recently partially isolated by Swanson of Winston-Salem, since this is not affected by sulfhydryl poisons).

We know that the C_{11} oxygenated adrenal steroids cause storage and accumulations of liver and muscle glycogen. The breakdown of this polymerized glycogen into glucose directly or indirectly would be impaired by any agent, such as cortisone, which is a sulfhydryl depletor. Is it not reasonable to anticipate that the sudden resupplying of sulfhydryls through the agency of glutathione to these inhibited enzyme systems would break the restraint, releasing the phosphorylative glycogenolytic enzyme mechanisms thus causing a sharp landslide of new glucose into the organism, hurling the animal with an already impaired beta cell function into a seriously aggravated diabetic state?

I would ask Dr. Lazarow for his comments on this as a possible explanation for the unexpected diabetogenic effect of sulfhydryls in his animals.

DR. ARNOLD LAZAROW (Closing): I should like to add that time likewise modifies the course of diabetes in the rat. We have kept alloxan diabetic rats under observation for as long as two years. After 12 to 18 months of continuous hyperglycemia, glycosuria, anorexia, etc. some animals began to gain weight, the urine output fell, the glycosuria gradually disappeared, and the blood sugar returned to normal levels. The animals were clinically improved. Obviously there are a number of unknown host factors which must still be evaluated in diabetes.

In regard to Dr. Anderson's point that glutathione may act on some peripheral enzyme: it does seem possible that glutathione might potentiate steroid diabetes by activating a sulfhydryl enzyme. According to recent work by Sutherland the hyperglycemia which follows adrenalin injection is due to the activation of phosphorylase by adrenalin; normally only part of the phosphorylase which is present in the liver cell exists in its active form. Apparently the various enzymes in the liver which catalyze the synthesis and breakdown of carbohydrate are in such delicate balance that the activation of a single enzyme, i. e., phosphorylase, alters this balance and produces a breakdown of liver glycogen and an elevation in the blood sugar. Furthermore, sulfhydryl groups are necessary for phosphorylase activity. Since cortisone injection lowers the blood glutathione level, one might postulate that a portion of the tissue phosphorylase becomes inactivated in steroid-injected rats as a consequence of this decrease in tissue sulfhydryl groups. One might, therefore, expect secondary readjustments to take place in the enzyme balance within the cell. Finally, when glutathione is injected into a cortisone-diabetic animal in which the enzyme balance is readjusted, the reactivation of phosphorylase to normal values might induce glycogen breakdown and hyperglycemia, as is the case following adrenalin injection. Although the activation of phosphorylase by adrenalin in the normal animal is probably not dependent upon sulfhydryl groups, the sulfhydryl activation of phosphorylase in a cortisone-diabetic animal would nevertheless have an adrenalin-like effect. Adrenalin injection likewise increases the hyperglycemia and the glycosuria in diabetic (depancreatized) dogs. The failure of glutathione to potentiate the glycosuria in chronic alloxan-diabetic rats would also be expected for in these animals the tissue sulfhydryl is not depressed and therefore glutathione should not activate phosphorylase. I do not mean to imply that phosphorylase must be the enzyme which is activated by glutathione, but it may be.

As for the source of the excreted sugar, it seems doubtful that there is sufficient glycogen stored in the liver of a 300-gm. rat to account for a glycosuria of 5 gm. However, an activated phosphorylase in the presence of an altered enzyme balance might prevent the deposition of ingested glucose (as glycogen) in both the liver and muscle. This might be sufficient to account for the hyperglycemia and glycosuria.

Hypoglycemia

Russell M. Wilder, M.D.

NATIONAL INSTITUTES OF HEALTH, U.S.P.H.S., F.S.A., BETHESDA, MARYLAND

Less than a year after the discovery of insulin, I had the good fortune to be one of a group of physicians invited to Toronto to arrange an extended clinical investigation of the use of insulin. Consequently I was one of those who received the early lots of insulin.

At that time my colleague, Dr. Walter Boothby, was studying the calorigenic action of epinephrine. He had found that the injection of epinephrine provoked not only a quick rise in the level of blood sugar but even more quickly a precipitate 30 or 40 per cent elevation of the metabolic rate. No one at that time had made any effort to find out if insulin had calorigenic activity like that of epinephrine or thyroxin. The fact, or at least we then thought it was a fact, that insulin hastened the burning of sugar, made the question very pertinent.

I had been working with Dr. Boothby on other metabolic phenomena in diabetes and it was natural for us, when we received that first insulin, to measure the oxygen consumption and carbon dioxide excretion of the patients to whom we gave it. We soon found that an insulin injection would provoke a transient increase in the metabolic rate, but this happened only if and when the level of the blood sugar had fallen below the normal fasting level.

We were puzzled at first by this effect of insulin on the metabolic rate and so we staged an experiment using the nondiabetic person, Russell Wilder, as a subject. Now it happened in those years that I was a victim of ragweed hay fever and had been in the habit, in the ragweed season, of injecting myself with epinephrine to relieve asthmatic symptoms. I thus had experienced personally the palpitation, sweating and feeling of anxiety provoked by epinephrine. The metabolic mask was bound over my face; insulin, in a dose of 30 units, was injected; and every 10 minutes the expired air and the blood were analyzed, the former for carbon dioxide and oxygen, the latter for glucose. Nothing unusual was experienced at first, but shortly after the fourth 10-minute period I was conscious that my arteries were pounding and my pulse and respiration were accelerated, and that I was sweating and experiencing a feeling of anxiety which I associated with injections of epinephrine. It occurred to me that these symptoms might be due to epinephrine secreted by my own adrenal glands and that this could be a purposeful phenomenon designed to release sugar from the liver and thus prevent extreme depression of the level of blood sugar.

In another room, in the meantime, Dr. Boothby had been receiving up-to-the-minute reports of the results of the analyses of the blood and the expired air. He was plotting these (Figure 1), and was struck by the similarity of the rapidly rising metabolic rate to that previously obtained when epinephrine was injected. He reached the same conclusion that I had, namely that the falling blood sugar had provoked release of epinephrine and that the epinephrine, not the insulin, was

Lecture delivered at meeting of New England Diabetes Association, Joslin Auditorium, New England Deaconess Hospital, Boston, Massachusetts, November 6, 1951.

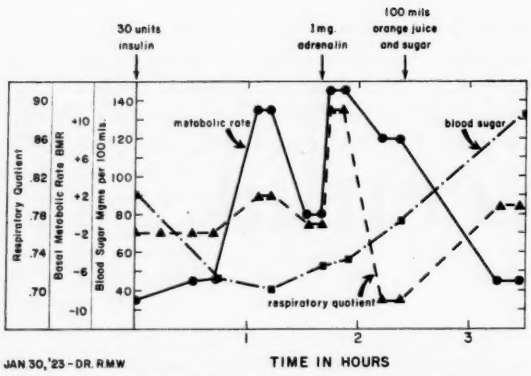


FIGURE 1 Metabolic rate, respiratory quotient and blood sugar levels before and following injection of insulin

responsible for the calorigenesis which was observed.

These observations were included with others in my report to the Insulin Committee in Toronto. Before they were published,[1,2] I gave a lecture in Boston, during which I reported on these studies. Dr. Walter Cannon, of blessed memory, was seated in the front row, and when I came to the account of the calorigenic effect of the hypoglycemia provoked by insulin I could clearly see that he was manifesting symptoms of epinephrinemia.

"The twin sisters, clinical observation and laboratory experiment, have walked in the field of diabetes very closely hand in hand." I am paraphrasing now from a friend and colleague in King's College, London, Dr. R. D. Lawrence.[3] Sometimes one has led, sometimes the other. But whichever led, the other soon proceeded to further progress to their mutual benefit and stimulation. We clinicians must gratefully acknowledge that the physiologist or biochemist usually has been out in front, but I take no little pleasure in the good fortune which was mine on that occasion to sow a seed in such a fertile soil as Professor Cannon's ear. He was working at the time with the denervated dog's heart and very soon thereafter could provide effective evidence of release of epinephrine by hypoglycemia. Thus another link was forged in the chain of balanced reactions whereby homeostasis is maintained in what Cannon later called the *Wisdom of the Body.*

It was shortly after announcing his and Dr. Best's discovery of insulin that Dr. Banting told me of their indebtedness to Mann and Magath, who only a year before had described the symptoms and fatal consequence of the hypoglycemia which they had induced in dogs by total removal of the liver. The symptoms could be arrested and the lives of the hepatectomized dogs could be prolonged by injecting glucose. Had it not been for this knowledge, Banting and Best would probably have attributed what they later called the insulin reaction, and which they saw when using their pancreatic extracts, to a toxic property of the extracts. Others who had investigated pancreatic extracts in earlier years may have made this mistake. Otherwise insulin might have been discovered ten or twenty years earlier! But of course we must remember that Banting and Best had available a micro-method for blood sugar analysis which their predecessors lacked.

Among the early visitors to the Toronto Laboratories when Drs. Banting, Best, Macleod and Collip, and their clinician associates Drs. Campbell and Fletcher, were pioneering with the early lots of insulin, was Dr. Seale Harris of Birmingham, Alabama.[4] He was quick to recognize that the symptom complex induced by insulin hypoglycemia was not unlike that which he had seen occurring spontaneously in certain of his patients. Soon thereafter he began reporting cases of unstable blood sugar. When the blood sugar levels fell, the patient became hungry, weak, tremulous and anxious, with hyperpnoea, tachycardia, sweating and occasional diplopia. Putting two and two together, Dr. Harris came to the conclusion that the episodes of hypoglycemia suffered by the patients in these cases were induced by an excess of insulin secreted by the pancreas. Consequently he came to diagnose this symptom complex as hyperinsulinism or dysinsulinism.

The conclusions reached by Dr. Harris were unacceptable to many because it was recognized by them that hypoglycemia and the symptoms which accompany it could result from several abnormalities in which the pancreas was not involved. Among such abnormalities were hypopituitarism, hypoadrenalism, some organic lesions of the central nervous system and some diseases of the liver, notably von Gierke's disease, so-called glycogenosis.

In 1927 a patient came to the Mayo Clinic presenting symptoms like those provoked by an excessive dose of insulin. However, he had had no insulin. I recently had read an article by Wagner and Parnas of Vienna that contained a report of glycogenosis in the case of a child. I was therefore on the lookout for such cases; and when this man was brought to my attention I thought at first that he might have this disease. However, our studies of the case did not bear out this supposition. Later, when the abdomen was explored at the patient's insistance and mine, a cancer of the pancreas was encountered. In the liver were a number of metastases. A bit of tissue was obtained from one of these and ex-

amined microscopically. It appeared to be composed of pancreatic island cells which looked like beta cells. The patient died some four weeks later. Necropsy was permitted, and extracts were obtained from the metastatic cancer, as well as from the tumor in the pancreas. Both extracts lowered the blood sugar when injected into rabbits; that from the metastases possessed activity representing an insulin content of not less than 40 units for each 100 grams of tissue. The case was reported jointly with Dr. Frank Allan, who was with us at that time, the chemist Dr. Marschelle Power, and the pathologist Dr. H. L. Robertson.[5]

This experience alerted us to look for cases of tumor of the pancreas with insulin activity, and before long more insulomas were discovered by ourselves and others. Some of them were malignant, others were benign. When these could be removed, the patients' episodes of hypoglycemia would completely disappear. However, there were other cases in which exploration would reveal no tumor. In some of them a second operation or necropsy would eventually reveal the presence of a tumor, but not in all. Especially confusing was a larger group of cases in which the patients' symptoms usually were less severe, cases resembling those described by Dr. Seale Harris. Operative search for insuloma in such cases was almost always fruitless.

Eventually we came to recognize that the patients in very many of these milder cases presented instability not only of the level of blood sugar but also of the vasomotor system—vasomotor instability not infrequently accompanied by emotional instability. A very few turned out to be malingerers, diabetic patients, nurses, or others acquainted with the use of insulin, who were purposely but surreptitiously injecting themselves with overdoses. Such malingering can be detected most conclusively by introducing a minute amount of radioactive iodine into the insulin container and later checking on the patient's urine with a Geiger counter. A fellowship assistant had that bright idea. Usually, however, the insulin reactions of malingerers are quite severe so that they resemble more those of patients with insular tumors.

It was also noted that the patients in these milder cases almost always developed their "reactions" in the daytime, three hours more or less after a meal, never at night, and never before breakfast. We had somtimes seen reactions which resembled theirs in diabetic suspects given a glucose tolerance test. The curve of the blood sugar level in such cases would rise more abruptly than is customary and later fall well below the base line. Furthermore, the patients in these milder cases would recover from their episodes of hypoglycemia spontaneously and rather promptly. This contrasted sharply with the behavior of the patients who had insulomas and who recovered from their episodes only after hours, if at all, unless they were given sugar.

So we introduced a diagnostic test—a fasting test which proved useful for separating the goats from the sheep. The patients were deprived of food from one evening's meal until the evening meal of the second day thereafter. Drinking water was permitted, but, because nicotine may stimulate the sympathetic nervous system, tobacco was prohibited. The level of blood sugar was examined every six hours and also whenever any symptoms developed. Exercise was restricted. The patient could be clothed and out of bed, but remained in his room under continuous surveillance.

The fasting test revealed that most of the patients in whom insulomas were detected later by the surgeon developed severe signs of hypoglycemia within from 6 to 36 hours. A few went longer without symptoms, but their blood sugar levels were down to 50 mg. per cent or lower by the second day or earlier. The other patients, those with milder symptoms and other instabilities, would behave quite differently. The level of their blood sugar would fall to 60 or 70, but it would not go any lower throughout the test period. Consequently these patients had no symptoms during fasting.

We called this "neurogenic hypoglycemia." Such cases can be detected also by a glucose tolerance test to which the patient usually, but not always, will respond with a more abrupt than normal rise in the level of blood sugar, followed in 3 hours or thereabouts by a fall to 60 mg. per cent or less. At that time they develop symptoms which, on occasion, are severe. However, the glucose tolerance test is less helpful for differential diagnosis than the fasting test, for sometimes patients with insuloma will respond with a similar sharp elevation and subsequent excessive fall of the level of blood sugar.

However, even though patients with hypoglycemia of the neurogenic type have no tumors or other hyperplasia of their islet tissue, we have not as yet excluded possible excessive function of their histologically normal beta cells. It is known that hyperglycemia provokes excretion of insulin by these cells. It has been supposed by certain scientists, although proof of this has not as yet appeared, that these cells also can be activated by the vagus nerve. In either case, Dr. Harris would be justified in his conclusion that the hypoglycemia in these cases was insulogenic. He, therefore, would be correct in diagnosing this as dysinsulinism.

However, it also is possible that either the stimulus of hyperglycemia or neurogenic stimuli are directed at the liver rather than the pancreas, and that in consequence this organ fails in its normal function of adding sugar to the blood from its glycogen reserves when the level of blood sugar falls. In that case excessive insulin would not be involved, and the designation insulogenic hypoglycemia would be incorrect.

This question, up to now, has not been answered for lack of a method to determine satisfactorily the amount of insulin in circulating blood. The technical difficulties involved in an assay of the blood for insulin can best be appreciated by recalling that the totally depancreatized man—and several patients are surviving now who for one reason or another have had the pancreas removed —requires only about 30 units a day. According to Waters and Best,[6] even if we assume that this insulin is equally diffused through the fluids of the extracellular compartment and that none of it is bound by cellular membranes, it would represent in a man weighing 60 kg. no more than a concentration in the order of one or two ten thousandths of a unit per cc. of blood, or 2×10^{-4}. How can such minute amounts be measured? It seems, however, that a method for doing this is right around the corner.

It will be recalled that insulin preparations formerly were assayed by injection into rabbits, and that a unit originally was defined as the amount of insulin necessary to provoke convulsions in a rabbit of a certain weight. As little as 0.01 units is convulsive for a mouse and less than this will lower the level of blood sugar to a detectable degree. In 1938, Hemmingsen and his associates in Sweden found that removing the adrenals of the mouse would increase its sensitivity to insulin about 5 times, so that 0.002 of a unit was detectable.[7] Gellhorn and others in 1941, at the University of Minnesota, found that hypophysectomy and adrenomedullectomy increased rat sensitivity to such a degree that 0.0002 units was detectable.[8] This was getting close to what might be required to assay the insulin in the circulating blood, but the question then arose as to whether insulin secreted by the rat's own pancreas was or was not affecting the results.

To settle this matter Dr. Evelyn Anderson and her associates alloxanized rats, and then removed the adrenal medullas, and subsequently the pituitaries.[9] Such animals proved so sensitive that only 0.125 milli-units (little more than 0.0001 units) of insulin produced detectable effects. The lowering of the blood sugar by larger doses was proportionately greater, as is shown by the chart from her report reproduced in Figure 2. A straight line relationship is observed between the logs of milli-units of insulin and the depression of blood sugar. Using this sensitive preparation, she and her associates obtained positive results from perfusion of the rat's pancreas in vitro, provided the pancreas of the rat was stimulated by perfusing sugar; but negative results (no evidence of insulin) when the sugar content of the perfusate was low. She also found that giving growth hormone would inhibit the stimulating effect of the perfusions of sugar.[10, 11]

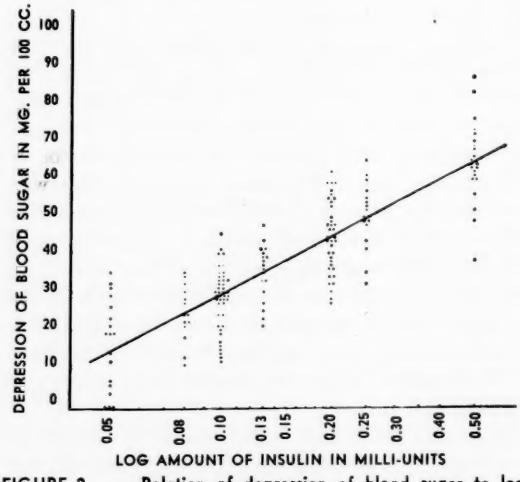


FIGURE 2 Relation of depression of blood sugar to log milli-units of insulin. Anderson, et al. [9, 10]

At this point I would like to refer to the recent work of Dr. Joseph Bornstein, a research fellow of the Baker Memorial Institute of Melbourne, Australia.[12] I have been rather out of touch with diabetes literature for the past year or so and did not know about his studies until I met him at Kings College, London, last June, through the kindness of Dr. R. D. Lawrence. Dr Bornstein is a jump or two ahead of everyone. Using rats which he has made diabetic with alloxan and has then hypophysectomized and finally adrenalectomized, he can detect as little as 0.05 milli-unit, or one twenty-thousandth of a unit, of insulin or even less. The depressions of the level of blood sugar obtained by him are proportional to the dose of insulin injected (Figure 3), a straight line relationship between the logs of insulin and the depression of the blood sugar. This result is exactly comparable to that of Dr. Anderson. However, he has gone much further. His controls are good and the results are quite impressive. The procedure is time consuming; nevertheless he has now made many determina-

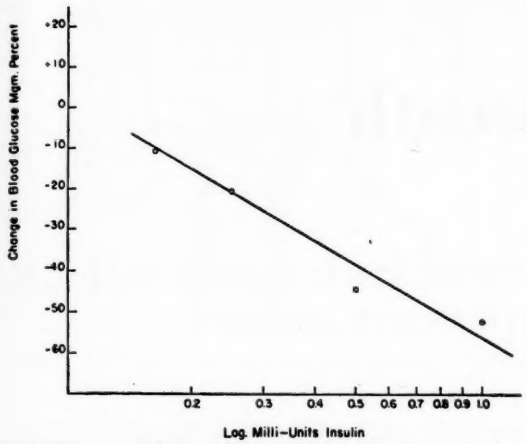


FIGURE 3 Relation of depression of blood sugar to log milli-units of insulin. Bornstein [11]

tions of the insulin content of circulating blood in normal persons before and after giving them sugar, in several diabetic patients, and in two patients with insulin-producing tumors.

Time does not permit a full review of Dr. Bornstein's observations. Briefly it appears that the amount of insulin in the circulating blood of 14 normal fasting subjects was detectable, but only barely so—from 0.025 to 0.05 of a milli-unit per cc. When sugar was injected the amount increased to peak levels, which ranged from 0.28 to 0.34 milli-units, or 0.0003 units per cc. The peak was attained at about 2½ hours after the glucose was injected, considerably later than the peak of the blood sugar curve. After that the fall was fairly rapid. In five cases of severe diabetes the values for insulin were zero, both before and after giving sugar to the patient. In milder diabetes, most of them being cases recently discovered in obese women, insulin was detectable after giving sugar. The amounts found approached but usually were smaller than those found in normal subjects. There were 9 such cases; in them the peak values per cc. of circulating blood were 0.10, 0.13, 0.17, 0.19, 0.19, 0.20, 0.24, 0.29 and 0.32. In the two cases of insuloma with symptoms of hyperinsulinism the fasting values were many times those found in the fasting normal subjects, higher even than any peak values of normals after sugar.

Dr. Bornstein has not yet studied patients with what we have called neurogenic hypoglycemia, but he has developed a method with which I think it will be possible to decide whether in this type of case we are dealing with excessive insulin secretion or not. He has confirmed Dr. Anderson's observation that growth hormone inhibited the secretion of insulin by the pancreas, but is uncertain about the interpretation of this. He suspects that the failure of the blood of persons who have been given growth hormone as well as sugar to lower the level of blood sugar in his sensitive test animals might mean that the growth hormone stimulates the alpha cells to a secretion of hyperglycemic factor, thus masking the effect of insulin.

The only drawback to early and more extensive clinical application of this procedure is the tediousness of the preparation of the test animals. Mortalities are high and control injections of insulin in known amounts are required before and after testing the blood for assay. It appears, however, that short cuts may be possible so that soon we will be able to use this as a tool of clinical significance, to tell us not only whether or not the hypoglycemia we encounter in a given case is insulogenic, but also whether our diagnoses of diabetes mellitus are sound.

REFERENCES

[1] Wilder, Russell M., Boothby, Walter M., Barborka, Clifford J., Kitchen, Hubert D., and Adams, Samuel F.: Clinical observations on insulin. J. Metab. Research 2:701-28, 1922.

[2] Boothby, Walter M., and Wilder, Russell M.: Preliminary report on the effect of insulin on the rate of heat production and its significance in regard to the calorigenic action of adrenalin. Med. Clin. North America 7:53-56, 1923.

[3] Bornstein, J., and Lawrence, R. D.: Two types of diabetes mellitus, with and without available plasma insulin. Brit. Med. J. 1:732, 1951.

[4] Harris, Seale: Hyperinsulinism and dysinsulinism. J.A.M.A. 83:729-33, 1924.

[5] Wilder, Russell M., Allan, Frank N., Power, M. H., and Robertson, H. E.: Carcinoma of the islands of the pancreas. J.A.M.A. 89:348-55, 1927.

[6] Waters, E. T., and Best, C. H.: The importance of developing an accurate method for the estimation of insulin in the blood. Proc. Am. Diabetes A. 7:171-83, 1947.

[7] Hemmingsen, A. M., Nielsen, A., and Nielsen, A. L.: Effect of insulin on adrenalectomized rats and mice. Acta Med. Scandinav. Supp. 90:105-10, 1938.

[8] Gellhorn, E., Feldman, J., and Allen, A.: Assay of insulin on hypophysectomized, adreno-demedullated, and hypophysectomized-adreno-demedullated rats. Endocrinology 29:137, 1941.

[9] Anderson, Evelyn, Lindner, Erna, and Sutton, Virginia: A sensitive method for the assay of insulin in blood. Am. J. Physiol. 149:350, 1947.

[10] Anderson, Evelyn, and Long, J. A.: The effect of hyperglycemia on insulin secretion as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinology 40:92, 1947.

[11] —: Suppression of insulin secretion by the growth hormone of the anterior pituitary as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinology 40:98, 1947.

[12] Bornstein, J.: A technique for the assay of small quantities of insulin using alloxan diabetic, hypophysectomized adrenalectomized rats. Australian J. Exper. Biol. & M. Sc. 28:87-91, 1950.

Acetone in the Breath

A STUDY OF ACETONE EXHALATION IN DIABETIC AND NONDIABETIC HUMAN SUBJECTS

Margaret J. Henderson, M.A., Beatrice A. Karger, M.A., and Gerald A. Wrenshall, Ph.D.*

BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH
UNIVERSITY OF TORONTO

INTRODUCTION

While it has long been suspected that free acetone may be a physiological metabolite, experimental evidence for its presence in nonfasting normal human subjects has remained inconclusive. This is probably due to the lack of specificity of known methods for determination of minute amounts of acetone in blood and urine (Weichselbaum and Somogyi, 1941, and others), for if free acetone is present in these fluids, it is there normally in very low concentration.

Where higher concentrations of acetone are present, however, as in the uncontrolled diabetic subject, its identity can readily be established in blood, urine and exhaled air. Widmark (1920) concluded that passage of the free acetone of blood into the alveolar air of diabetic subjects takes place in conformity with the laws of diffusion.

We have undertaken a study of the free acetone content of the exhaled air from nonfasting diabetic and normal subjects, using two widely dissimilar yet highly sensitive methods for the determination of free acetone in aliquots of the same sample of condensed exhaled vapor. One of these, a physical method using a recording mass spectrometer, was mass-specific for acetone. The second was the chemical micromethod of Greenberg and Lester (1944).

* Present address: Department of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio.

METHODS

Collection of Exhaled Air

An attempt to collect acetone from exhaled air by cold condensation was first reported by Frerichs in 1883. Salomon, a worker in his clinic, had caused a diabetic patient to breathe through a series of bottles surrounded by an ice-salt mixture, but had failed to detect acetone in the condensate. The first successful quantitative collection method which could be applied to human subjects was developed in 1898 by Mueller. He used four Woulf flasks half-filled with distilled water and immersed in an ice-salt mixture.

Our method of collection employed a series of liquid air traps in which the exhaled water vapor, carbon dioxide, and acetone were condensed. Figure 1 shows a schematic diagram of the apparatus as finally evolved, not drawn to scale. The subject inspires outside air† through large-bore copper tubing attached by a short rubber connection to the inlet valve of a metabolor face mask, M. He then expires through the outlet valve of the mask into a wide-bore glass conduit which leads to a Pyrex condenser, C, immersed in liquid air in a Dewar flask, D. Glass tubing connects a second condenser to the first. Also attached to the first condenser is a vinylite bag, B, which makes possible the maintenance of a

†Outside air was found to contain considerably less acetone than laboratory air, the mean value of acetone per liter of outside air being less than 10 per cent of the mean value of acetone exhaled per liter in normal subjects.

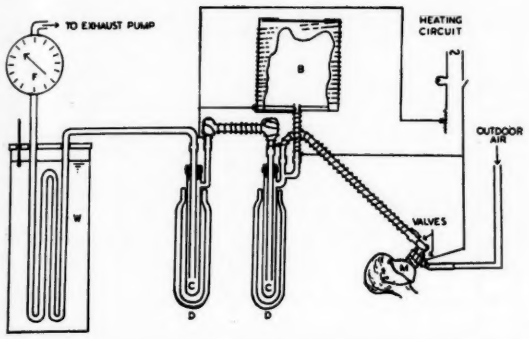


FIGURE 1 Diagram of apparatus for collection of exhaled vapors

steady flow through the condensers,* and in addition serves as an index of the speed of pumping required. The conduits and bag are maintained at 40° C. to prevent any condensation except in the traps, and to rewarm the air as it passes between traps.† After passing through the condensers, the uncondensed components of the exhaled air are drawn through several turns of copper tubing in a large container of water, W, to stabilize the temperature before their volume is read on a flowmeter, F. A pump beyond the meter draws the air through the system continuously, and the rate is adjusted according to the amount of air in the vinylite bag.

At the time the study was begun, no reference to a condensation method of collecting acetone using liquid air had been found in the literature, so the efficiency of this procedure had to be investigated. Knowing the mass of condensate in the two condensers, m_1 and m_2, and assuming that the fraction of the entering vapor condensed in each trap was the same, the total mass, M, of condensate passing into the condenser system could be calculated from the equation

$$M = m_1^2 / (m_1 - m_2).$$

This calculated total mass was found to be from 95 to 99 per cent of the actual mass collected in a series of 79 tests in which three condensers were used instead of two.

When similar determinations were made to calculate the theoretical recovery of acetone itself, it was found that for low acetone values the calculated yield agreed with that found experimentally, but at high acetone levels the actual recoveries were lower than the theoretical ones. A closer approach to the theoretical acetone yield was obtained using a trap containing 2, 4-dinitrophenylhydrazine at the end of the condensing system. However, in our survey, the calculated values based on collection from two liquid air condensers were used throughout.

After the experimental work had been terminated, references in recent literature were found to methods of trapping vapors which included both of the foregoing ideas. Price and Rittenberg (1950) had used two ice-cooled phenylhydrazine traps to collect acetone from the exhaled air of rats. Cadle, Rolston and Magill (1951) used a series of three Dewar flasks filled with a dry ice and isopropyl alcohol mixture followed by a trap immersed in liquid nitrogen to collect volatile atmospheric contaminants. They later simplified this system to a coil immersed in the dry ice mixture, followed by a U-tube in liquid nitrogen. One arm of the U-tube was packed with aluminum washers, which increased the condensation efficiency by 30 per cent.

Analysis of Acetone

The chemical method for analysis of acetone was that of Greenberg and Lester (1944). This involves the formation of acetone 2, 4-dinitrophenylhydrazone, its extraction with carbon tetrachloride, and its colorimetric determination. The latter was done using a Coleman Junior spectrophotometer at 420mμ.

In the physical method of analysis, vapor of the aqueous condensate to be analysed was passed into the ionization chamber of a recording 90° mass spectrometer similar in design to that of Graham, Harkness and Thode (1947). Approximately 1 ml. of chilled aqueous condensate, to which a fixed concentration of chloroform had been added to serve as an internal standard, was admitted into an evacuated vapor bulb with a flash boiler at its base and a large cold condensing surface. Equilibrium was quickly established between condensate and saturated vapor filling the system and the heated mass spectrometer capillary leak. A very stable vapor-feed pressure was maintained by holding the condenser temperature at a suitably low value (5° C.).

It was established by experiment that a linear relationship existed between concentration of acetone in the aqueous phase and peak height for the four most prominent lines of the mass spectrum for acetone over a 10,000-fold range of concentrations. The parent and the most prominent peak (m/e 58 and 43, respectively)

*A steady flow of exhaled air through the condensers was found to give more efficient collection than the normal jerky expiration stream.

†Rewarming the air melts any frozen particles which are dislodged from and escape the first trap, and also ensures that vapors enter both traps under similar conditions, as required for the calculation of the total mass of condensate.

were used throughout the analyses in comparisons of standard and unknown samples. Peak heights in each reversed scan of a given sample were always measured relative to the height of the chloroform peak at m/e = 47. The condenser receptacle was vacuum-dried between runs, and was rinsed with a small amount of the next sample to be analysed before the actual analysis was made. While the above method required relatively large samples, this was compensated for, at least in part, by reducing the effectiveness of "memory" errors in the mass spectrometer. The mass spectrometric method is mass-specific for acetone, and due to the method of collection and analysis of exhalate, any substance which might be present as a mass-specific contaminant must also be volatile.

An indication of the specificity of the method was obtained by comparing the values found for the concentration of acetone in the same aqueous condensate of human breath by mass spectrometer with those found by the microchemical method. The degree of correspondence between results is shown in Figure 2.‡ This statistically significant correlation observed with such totally different analytical methods supports the belief that the substance measured is acetone.

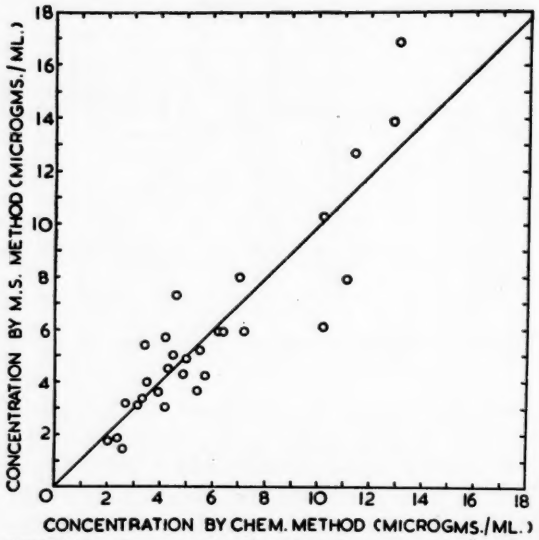


FIGURE 2 Concentration of acetone in aqueous condensates from human breath. Determined by chemical (chem.) method and compared with corresponding values determined by mass spectrometer (m.s.)

RESULTS AND DISCUSSION

Normal Human Subjects

Determination of acetone in exhaled air seemed particularly suited to the investigation of acetone levels in normal human subjects, since it circumvented difficulties usually found in detecting minute amounts of free acetone in blood and urine. Weichselbaum and Somogyi (1941) in describing a method for determination of ketone bodies in blood, stated that existing methods, including their own, lacked the desirable degree of precision. They found the total ketone bodies in nonfasting human plasma (expressed as beta-hydroxybutyric acid) ranged from 0.33 to 0.94 mg. per 100 cc., with a mean of 0.5 mg. Their group consisted of 16 persons. Behre (1931) studied urinary ketones in normal humans, and found the ketone bodies (from acetone and diacetic acid) ranged from 0.10 to 0.66 mg. per 100 cc. urine from 24-hour samples, with a mean of 0.25 mg. Her group consisted of 12 individuals, and samples were collected over 32 daily periods. Behre also stated that study of a large number of unselected urine samples indicated the normal concentration of urinary acetone and diacetic acid was below 0.5 mg. per 100 cc., but the actual number of persons was not given. Hubbard (1920) found that acetone exhalation in 22 normal humans ranged from 0.14 to 0.52 mg. per hour.

Our study of acetone in exhaled air included two groups: the first consisted of 57 subjects; and the second, studied a year later after some changes to the collection apparatus, and by a second investigator, consisted of 49 subjects. The persons were all healthy individuals, nonfasting, and were tested at different times throughout the day. The collection period was usually about one hour, during which the subject rested on a cot in the laboratory. Table 1 shows the acetone values in these two groups separately, and also, since statistical analysis showed no significant difference between them, their combined value.

The method of expressing acetone exhalation used in the table, micrograms per gram of condensate per square meter of body surface, was used rather than the more common one of acetone exhaled per hour because the former is independent of such variables as respiration rate and body size. Exhalation of acetone could have been expressed equally well in micrograms per liter of exhaled air, as a linear relation was found to exist

‡Coefficient of correlation, $r = 0.96$, and the equation of the linear regression line is

$$Y = 0.99\ X - 0.01$$

where Y = acetone in micrograms/ml. obtained by mass spectrometry and X = acetone in micrograms/ml. obtained by microchemistry. Test of significance gives "t" value of 18.2, $P < 0.001$.

TABLE 1 Acetone exhalation in human subjects (micrograms/gram condensate/square meter of body surface) and significance of differences between groups

Description of subjects	No. of subjects	Mean	Range	Standard Deviation	Standard Error	t	p
Normal Group 1	57	4.6	1.3 — 11.8	2.2	0.29	0.322	0.7
" " 2	49	4.7	1.3 — 12.7	2.6	0.37		
Diabetic Group 1	39	7.7	2.3 — 34.9	6.3	1.0	1.59	0.1
" " 2	31	10.8	3.2 — 42.6	9.8	1.8		
Total—Normal	106	4.6	1.3 — 12.7	2.4	0.27	5.32	<0.001
" Diabetic	70	9.1	2.3 — 42.6	8.2	0.98		

between this value and the same data expressed as micrograms of acetone per gram of condensate, indicating constant efficiency of condensate collection. The linear relation between micrograms of acetone per hour and micrograms per gram of condensate was not as well marked, reflecting a variation in rate of exhalation. Factors such as change in rate of breathing or increased resistance to expiration altered the rate of acetone exhalation, but not the concentration of acetone per gram of condensate or per liter of air. Therefore it seemed preferable to express acetone as a concentration rather than as a rate. The finding of acetone in the exhaled air of all normal subjects tested seemed to indicate that it was a normal metabolic product, and on this assumption we have calculated acetone exhalation per square meter of body surface.

However, to permit comparison of our values with those of Hubbard (1920), it was also necessary to express the results as rates of acetone exhalation. The range found in 106 subjects was from 0.029 to 0.23 mg. acetone per hour. Hubbard, using a collection period of 10 minutes as compared with ours of 60 minutes, found the acetone exhalation rate in 22 normal people ranged from 0.14 to 0.52 mg. per hour.

Within the group of normal subjects, statistical analysis indicated that females exhaled significantly higher amounts of acetone, expressed as micrograms per gram condensate per square meter of body surface, than males (Table 2). This observation in nourished humans supports that of Deuel and Gulick (1932) who reported that fasting ketosis developed more rapidly and was more intense in normal females than in normal males. No significant difference was found between persons working in the department and those from outside the building (Table 2). No trend in acetone exhalation with age was seen (Figure 3).*

The variations in acetone exhalation which were found within the normal group could be due to nutritional, physiological, or psychological factors. The time of day (Behre, 1931), the relation of food intake (Somogyi, 1942), even the state of mind of the subject (Hinkle, Conger and Wolf, 1950), have been claimed to influence acetone levels.

The influence of diet was investigated in this survey. In six subjects, examined weekly over periods of from one to four months, an increase in weight was accom-

*Linear regression line of acetone exhalation on age is $Y = 4.68 - 0.00179X$. "T" test shows that slope does not differ significantly from zero ($P > 0.9$), implying that there is no relation between acetone exhalation and age.

TABLE 2 Acetone exhalation in human subjects (micrograms/gram condensate/square meter of body surface) and significance of differences between groups

Description of subjects	No. of subjects	Mean	Standard Error	t	p
Normal					
Male	42	4.0	0.28	2.22	0.03
Female	64	5.0	0.33		
Departmental	63	4.9	0.31	1.26	0.2
Nondepartmental	43	4.3	0.35		
Diabetic					
Male	32	7.7	1.3	1.35	0.2
Female	38	10.3	1.5		
Hospitalized	12	10.4	1.5	0.184	0.8
Nonhospitalized	19	11.1	2.8		

panied by a decrease in acetone exhalation, and a decrease in weight by an increase in acetone exhalation. In a control subject on a normal diet, no marked changes in weight or acetone exhalation occurred. That acetone exhalation was influenced mainly by changes in the proportion of carbohydrate in the diet was shown in three subjects who ingested no carbohydrate for periods of from one to seven days. Acetone exhalation increased about five-fold after one day in all cases, and in the one experiment which lasted seven days it had increased one hundred-fold. Termination of the carbohydrate-free diet by glucose in one of the these experiments resulted in a roughly exponential decrease in acetone exhalation toward normal, about half the pre-glucose value being reached by the end of the third hour.

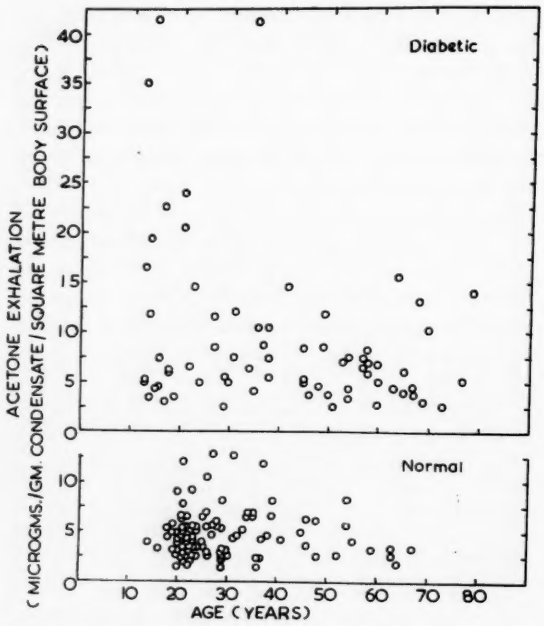


FIGURE 3 Acetone exhalation as a function of age

Diabetic Subjects

The odor of acetone on the breath of subjects in diabetic coma was one of the earliest stimuli to the investigation of acetone metabolism, and many studies of ketone levels have been made in diabetics.

The present study, as in the case of nondiabetics, covered two groups of people over a period of two years. The first group consisted of 39 nonfasting treated diabetic subjects who came to the laboratory from their work or homes at varied times throughout the day. The

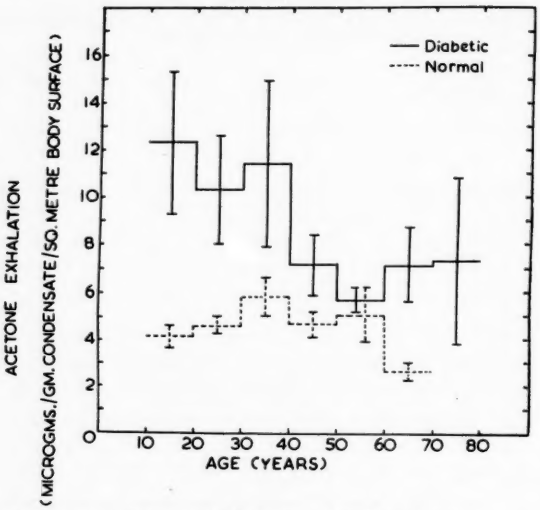


FIGURE 4 Acetone exhalation as a function of age

second group consisted of 31 diabetic subjects, 19 of whom were as above, and 12 of whom were hospitalized diabetic patients who were brought to the laboratory a day or two before discharge from hospital. Table 1 shows acetone values in these two groups separately, and also, since statistical analysis showed no significant difference between them, their combined value. It will be seen that the range of values is much wider in diabetic than in normal subjects. Diabetic humans, even though treated, exhale greater amounts of acetone than do normal humans.†

Within this diabetic group, females exhaled numerically greater amounts of acetone than males, but the difference was not significant when analyzed statistically (Table 2). No difference was found between hospitalized and non-hospitalized subjects (Table 2). However, there appeared to be a trend in acetone exhalation with age, for the highest observed values were found to occur in persons under 40 (Figure 3).‡ In Figure 4 the mean values with their standard errors for each 10-year age

†It is recognized that a downward trend with increasing age in acetone exhaled exists for diabetic subjects, and that such a trend will increase the apparent standard error of the mean for all diabetic subjects regardless of age. In spite of this, it is found by "t" test that the mean exhaled acetone for diabetic subjects of all ages is significantly higher at the 0.1 per cent level than for normal subjects of all ages.

‡Linear regression line of acetone exhalation on age is $Y = 14.2 - 0.126X$. "T" test shows that slope differs significantly from zero ($P = 0.01$), implying a relation between acetone exhalation and age.

group show the downward trend with age in diabetic subjects, and the lack of such a trend in normal subjects.

The tendency of young diabetics to more severe ketosis is in accord with the findings of various workers. Himsworth and Kerr (1939) reported that diabetic patients could be divided into two groups, insulin-sensitive and insulin-insensitive, and that the insulin-sensitive patients were mainly younger and showed a more pronounced tendency to develop ketosis. Wrenshall, Bogoch and Ritchie (1952) found that the insulin extractable from the pancreas at autopsy of growth-onset diabetic patients was very low,* but this was not so in about 80 per cent of maturity-onset diabetic patients. Bornstein and Lawrence (1951 a and b) report that levels of available plasma insulin in all three growth-onset diabetic subjects of their series were below the lower limit of their method of assay. These subjects all showed ketosis and progressive weight loss prior to the administration of insulin.

Lack of endogenous insulin in young subjects would make them dependent on exogenous sources, and this could result in periods of poor as well as of good diabetes control, with accompanying variations in ketone levels. This situation would reasonably account for both the occurrence of occasionally very high acetone exhalation values and the large dispersion found in younger age groups as compared with older subjects of the same series. Older treated diabetic subjects, most of whom probably have a continuous, although restricted, endogenous supply of insulin in addition to that which was administered, did not show such marked variations.†

Further evidence pointing to the difference between young and old diabetic subjects was found in the group tested during the second year of the survey. Blood sugar levels were determined at the end of each collection of exhaled air, and the higher levels were found mainly in younger diabetic subjects. When an attempt was made to correlate acetone exhalation with blood sugar levels it was found that in growth-onset diabetic subjects there was a degree of positive linear correlation which was significant at the 5 per cent level by "t" test, but in maturity-onset diabetics there was no significant correlation.

*By "low" is meant 10 per cent or less of the average extractable insulin of pancreas found in nondiabetic controls at autopsy.

†Two important differences exist between the data reported by Bornstein and Lawrence (1951 a and b) and those presented in this paper. While the diabetes of their subjects was untreated at time of observation, that of all subjects of the present series was under therapy. The ages reported by Bornstein and Lawrence thus represent those at diagnosis of diabetes, while in this series the ages represent those at measurement of acetone exhalation. The same differences exist between the data of Bornstein and Lawrence and those of Wrenshall, Bogoch and Ritchie (1952) and these should be borne in mind when comparisons are made.

SUMMARY

1. Acetone exhalation in human subjects was investigated using a collection method dependent on the condensation of exhaled vapors in liquid air traps, and subsequent analysis of the condensate by chemical and mass spectrometric methods.

2. Normal nonfasting individuals were found to exhale demonstrable and fairly characteristic amounts of acetone.

3. Diabetic nonfasting subjects were found to exhale significantly higher amounts of acetone with a much wider range of variation in values.

4. Normal female subjects were found to exhale significantly higher amounts of acetone than normal male subjects. In the diabetic group, although the acetone level in females was numerically higher than in males, the difference was not significant.

5. A trend was seen for young diabetics to exhale more acetone than older ones. This was not seen in nondiabetic individuals.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Professor C. H. Best whose interest and support made this survey possible; to Dr. Bruce Casselman and Dr. Charles Vuylsteke whose help was invaluable during the early stages of the project; to Dr. W. T. W. Clarke who arranged for hospitalized diabetic patients to participate; to those members of the Diabetic Association of Ontario who volunteered to act as subjects; and to all those who acted as nondiabetic controls and who took part in the dietary experiments.

The generous help given by Professor H. G. Thode of McMaster University on problems relating to the mass spectrometer is gratefully acknowledged.

This research project was supported by funds from the National Research Council of Canada.

REFERENCES

Behre, J. A.: Studies in ketone body excretion. I. Daily variations in the ketone bodies of normal urine and the ketonuria of short fasts, with a note on diabetic ketonuria during insulin treatment. J. Biol. Chem. 92:679-97, 1931.

Bornstein, J., and Lawrence, R. D.: Two types of diabetes mellitus, with and without available plasma insulin. Brit. M. J. 4709:732, April 7, 1951. (a.)

(Continued on page 200.)

REPORT OF THE GLOUCESTER DIABETES STUDY

Evaluation of a Method of Self-Testing for Diabetes

Vlado A. Getting, M.D.

COMMISSIONER, MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH, BOSTON

Howard F. Root, M.D.

CHAIRMAN, DIABETES COMMITTEE, MASSACHUSETTS MEDICAL SOCIETY, BOSTON

Hugh L. C. Wilkerson, M.D.

CHIEF, DIABETES SECTION, DIVISION OF CHRONIC DISEASES AND TUBERCULOSIS, U.S.P.H.S., BOSTON

Herbert L. Lombard, M.D.

DIRECTOR, DIVISION OF CANCER AND CHRONIC DISEASES, MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH, BOSTON

Victoria M. Cass, M.D.

ASSISTANT DIRECTOR, DIVISION OF HOSPITALS, MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH, BOSTON

A need exists for a practical and economical method of identifying the numerous, undiscovered cases of diabetes mellitus. It has been estimated that in the Unites States there are approximately one million diabetics with the disease undiagnosed.[1] To discover these cases in their incipiency requires organized case-finding programs. Such programs usually are expensive undertakings, since they require special equipment and trained professional personnel. For this reason, a relatively simple, inexpensive procedure has been sought which could be used satisfactorily as a mass case-finding method.

Self-testing of urine is used successfully by certain groups of lay individuals. For the most part, these are persons with diagnosed diabetes mellitus who have been trained to employ a self-test method and to interpret correctly the results of their tests as an integral part of a regime for therapeutic control. Whether or not this same technique of self-testing may be employed successfully in communities as a case-finding technic has never been satisfactorily established.

The purpose of this communication is to report the results of a study designed to answer these questions: Is

it possible for large groups of lay individuals to perform accurately the self-test for sugar in urine samples? If so, do those whose tests indicate the presence of excess sugar in their samples seek further diagnostic studies? These were the basic questions which apparently had to be answered, in order to justify the use of the self-test method for mass surveys in diabetes detection. It must be emphasized that the study, conducted in Gloucester, Massachusetts over a two-month period, was not intended to locate new cases, but rather to measure the ability of a large group of people to perform a specific technique, to interpret correctly the results of their tests, and to act upon these results.

Gloucester is a community of approximately 28,000 persons. Its area of 26 square miles includes several distinct villages separated from each other by a few miles of roads. Racially, the community is divided into four groups—Italian, Portugese, Finnish, and "Old Gloucester Yankee" stock. Although in the summer months a substantial income is derived from a large influx of tourists, fishing is the principal year-round industry,

This project was undertaken by the Massachusetts Department of Public Health, the Diabetes Control Section of the United States Public Health Service and the Diabetes Committee of the Massachusetts Medical Society, with the cooperation of the medical staff of the Addison-Gilbert Hospital, in Gloucester. Through a grant from the Nordisk Insulin-fund to the American Diabetes Association, funds were provided to assist in carrying out the survey. This grant was secured through the interest and cooperation of Dr. Elliott P. Joslin.

METHOD OF STUDY

The Gloucester study was not a case-finding program but an evaluation of a community's ability to perform a specific procedure, i.e., the self-test for urine sugar. The first step was to secure public interest in and understanding of the program. For this purpose, a Citizens' Committee, composed of representatives of various racial, religious, social, labor, business and professional groups of Gloucester, was organized. Public interest in the program was stimulated by numerous newspaper articles, both on diabetes mellitus and on the proposed study, by programs on the local radio station, and by a film on diabetes control, exhibited at a Gloucester theatre. Moreover, a letter explaining the study was prepared and mailed by the Committee to the 8,000 householders of the city.

Concurrent with this publicity, an interviewing team (which was to conduct follow-up studies on those who participated in the program) received indoctrination regarding diabetes mellitus. A pretested 41-line questionnaire was designed for these subsequent studies. The interviewing team gained experience in its use by conducting a pretest on 100 individuals employed in a Boston office. The completed questionnaires on 2911 survey participants provide the source material for all analyses contained in this report.

With the cooperation of the Gloucester drugstores, self-testing kits were made available for public distribution. Each kit contained sufficient material to perform two urine tests and included printed instruction for the collecting and testing of specimens, with advice to report any "suspicious" findings to a physician. As these kits had been donated by a private firm for research purposes, no charge was made for them.* However, each person had to go to a drugstore and register by name, address and date, in order to obtain the kit. By means of this registry, the interviewing team was able to contact survey participants for follow-up studies regarding the use of the test material. It is appreciated that, had a charge been made for procuring the kits, not only the number and characteristics of the individuals in the cooperating group but also their responses might have differed from the present findings. Within four days following the appearance of the self-test kits in the drugstores the entire supply was exhausted.

EXTENT OF COMMUNITY PARTICIPATION

An accounting for the distribution of 3252 kits was obtained from the registration cards made out in the drugstores. The kits were distributed primarily to residents of Gloucester, and only about 5 per cent were received by the summer visitors. It is estimated that the surveyed population comprised about 20 per cent of the Gloucester population in the age groups 20 to 65, but the percentage was less under and over this age group.

The 1950 census was not available, but the population of Gloucester recorded in the four preceding censuses has not differed greatly, ranging from 24,046 to 24,862. The surveyed population probably included a somewhat smaller percentage of males than the Gloucester population. In 1940, males comprised 48.7 per cent of the Gloucester population, while they made up 46.6 per cent of the surveyed population.

In Table 1 is shown the distribution, by type of performance, of the 3252 persons responding to the community campaign to participate in the self-testing program.

*Assistance given by the Ames Company, Inc., of Elkhart, Indiana, is gratefully acknowledged.

TABLE 1 DISTRIBUTION OF REGISTRANTS—BY TYPE OF PERFORMANCE

Total number of individuals who registered for and accepted kits		3252
Number performing self-tests	1730	2911
Number not performing self-tests	1181	
Number of "lost persons" who could not be located for interview"		341

From the above table it may be seen that complete information could be obtained from 2911 persons relative to use or non-use of the self-test. Of this group 1730 (59 per cent) actually performed the test whereas 1181 individuals (41 per cent) failed to perform the test once they had obtained the material. Reasons for this failure are discussed later.

With the test employed in this study, sugar in the urine amounting to more than 0.2 per cent resulted in color changes ranging from green, olive green, tan, orange to brown, depending upon the amount of glycosuria.

The following instructions for interpreting and acting upon the results of the self-test were given in the instruction sheet included with each kit:

1. Blue means "negative"—no sugar.
2. Any other color means "positive," "suspicious," or sugar present.
3. If the color change was anything beyond green, the examinee was advised to report his findings to his physician in order that the cause of the glycosuria might be determined.
4. With a single green result, the examinee was advised to repeat the test on a second urine sample.
5. If the second test resulted in a color change of any sort, that is, if it was other than blue, the examinee was urged to notify his physician.

In a community-wide undertaking in which self-testing is employed as a screening device, the technical instructions must of necessity be brief, simple and definite. The categories of "suspicious" and "negative" results presented in Table 2 conform with the criteria used by the participants in this self-testing program.

RESULTS OF SELF-TESTING

Of the 1730 individuals known to have performed the test, 1526 persons, or 88 per cent, had results classified as "negative," and 98 persons, or 5.6 per cent had "suspicious" findings. The remaining 106 persons, or 6.2 per cent, could not be classified in either of the above categories (Table 2). The majority of this category were those who, after obtaining a green reaction with the self-test, failed to follow instructions, i.e., to repeat the test on a second urine sample.

The self-testing urine procedure, as well as any detection method based upon a single determination, appears to have certain inherent weaknesses. Even mild glycosuria should not be lightly passed over by the clinician. Some persons with this finding may appear at first to be nondiabetic, but upon long-term follow-up are found to have diabetes, as has been shown by Joslin, Root, and others.[2] Moreover, the single negative determination should not be used for the exclusion of diabetes, as has been pointed out by Beaser[3] and Harting.[4] These weaknesses are recognized as existing in the self-testing procedure as it has been employed here.

TABLE 2 RESULT OF SELF-TESTING BY 1730 INDIVIDUALS ACCORDING TO COLOR REACTIONS OBTAINED

Color Reaction		Known Diabetics	Other Examinees	Totals		
Test 1	Test 2	No. Persons	No. Persons	Number		Per Cent
Negative Group						
Blue	(Blue)	33	1405	1438	1526	
Green	Blue	1	87	88		88.2
Undetermined Group						
Green	——	0	98	98	106	
Green	Unknown	0	1	1		
Unknown	——	0	7	7		6.2
Suspicious Group						
Green	Green	8	67	75	98	
Yellow, Orange or Brown		5	18	23		5.6
Totals		47	1683	1730		100.0

TABLE 3 DISTRIBUTION OF "SUSPICIOUS" CASES SEEKING MEDICAL ADVICE BY RESULTS OF SELF-TESTING

Color Reaction		Cases with Suspicious Findings			Suspicious Cases Seeking Medical Advice	
Test 1	Test 2	Known Diabetics	All Others	Total Number	Number	Per Cent
Green	Green	8	67	75	18	24.0
Yellow, orange or brown		5	18	23	5	21.7
Totals		13	85	98	23	23.5

However, it is obvious that the self-testing procedure could be used more effectively if all those having results classified as "suspicious" (i.e., green, yellow, orange or brown reductions) secured diagnostic studies from physicians. The fact that the population under study failed in this respect is illustrated in Table 3.

Of a total of 98 persons with suspicious findings (and including 13 known diabetics) only 23 or 23.5 per cent visited their physicians for diagnostic follow-up studies; in other words, over three-fourths of this group, 76.5 per cent, failed to seek further advice. The inclusion of diagnosed cases of diabetes in these figures is a condition which could not be avoided, as no selectivity was employed in the choice of individuals wishing to participate in the survey.

INTERPRETATION

One of the most interesting aspects of the survey was the manner in which the examinees interpreted the results of their tests (Table 4). These interpretations were obtained in response to the interviewers, question: "What does the color result of your test mean to you?"

A negligible number of those who had had "negative" reactions believed they had diabetes. However, of the group of 98 persons with "suspicious" findings, 35 per cent interpreted their test results as indicating that they had either no diabetes or no sugar in blood or in urine, and only 23.5 per cent interpreted their positive tests as indicating a need for obtaining diagnostic studies to determine the cause of the glycosuria.

Another finding of interest, which also pointed up the inability of the population under study to perform mass self-testing successfully, was found within the group of 262 individuals each of whom had obtained a green reduction with the self-test. Ninety-eight (37 per cent) of those obtaining a green reduction failed to examine a second specimen as instructed.

Apparently a relationship exists between the number of examinees correctly interpreting their suspicious findings and the number of physician referrals. Only 23 (23.5 per cent) of those in whom the presence of diabetes should have been seriously suspected interpreted their results as indicating the need for further studies by a physician. The same number (23.5 per cent) did make a visit to their physicians because of their suspicious findings. It should be mentioned that within this group of 23 individuals, two were known diabetics who belived that because of these positive findings, further medical advice was required.

TABLE 4 INTERPRETATION OF RESULTS OF SELF-TESTS BY 1730 EXAMINEES

Interpretation of Results by Examinees	Neg. Results No. Persons	Unconfirmed Results No. Persons	Suspicious Results	
			No. Persons	Per Cent
"No disease" or "No sugar"	1518	49	34	34.7
Might have diabetes	1	6	22	22.4
Sugar in urine or blood	0	8	17	17.3
Repeat the test	2	36	0	—
See my physician	0	4	23	23.5
No opinion	5	3	2	2.0
Totals	1526	106	98	99.9

COMPARISON OF PERFORMERS AND NON-PERFORMERS

Of the 2911 individuals on whom complete follow-up studies were obtained, it was found (Table 1) that 1730 (59 per cent) performed the self-test while 1181 (41 per cent) failed to use the kits they had obtained. A comparison of these two groups was undertaken in an effort to determine what similarities and differences characterized performers when compared with non-performers.

With respect to age and academic levels, there was no significant difference. Forty-four per cent of the performers were males, as compared with 49 per cent of the non-performers. The two groups differed in respect to the reasons given for having secured the kit. Of those who actually self-tested, a larger percentage claimed

they obtained the kits because of a willingness to participate in a community endeavor, a fear of the disease, or the presence of diabetes mellitus in the family, than was found in the group who failed to perform the test. On the other hand, a smaller percentage of participants than of non-participants secured the kits because of family advice (Table 5).

TABLE 5 REASONS FOR SECURING KITS

	Non-Performers Per Cent	Performers Per Cent
Diabetes in self or family	8.2	11.1
Worry	5.6	9.3
Civic response	10.6	15.6
Recommended by physician, druggist or other individual	7.8	5.4
Recommended by family	27.8	16.0
Preventive measures	30.3	34.1
Curiosity	7.8	7.9
Other reasons	1.8	0.7
Totals	99.9	100.1

Apparently those who accepted the kits and performed the test actually had a closer association with diabetes than did those who did not use the kits. That is, a higher percentage of diabetes in their own or their spouses' families was found to exist in the group of individuals who performed the test (Table 6).

TABLE 6 PRESENCE OF DIABETES IN FAMILY OR SPOUSE'S FAMILY

	Non-Performers Per Cent	Performers Per Cent
Acceptor had diabetes	1.2	1.9
Acceptor had diabetes, and diabetes in family	0.2	0.8
Acceptor had diabetes, and diabetes in spouse's family	0.0	0.2
Diabetes in own family and in spouse's family	0.8	1.4
Diabetes in own family only	15.4	17.9
Diabetes in spouse's family only	6.5	8.2
No diabetes	76.0	69.7
Totals	100.1	100.1

Those performing the test also had a larger number of friends afflicted with diabetes than did those failing to self-test, the respective rates being 57 and 46 per cent.

When the 1181 individuals were questioned regarding their failure to use the kits, the most frequent answer was that they had "lost interest" in performing the tests. Nearly a third stated that they still intended to use the kits, but since these individuals were interviewed two to four weeks after the kits had been obtained, it is doubtful that they were or ever will be used. The next most frequent reason given for failure to use the kits was that they had mechanical or other hindrances. These hindrances included broken test tubes and droppers, and lost tablet reagents, but the primary hindrance was repeated failure to remember to do the test at the proper time after a meal. Slightly over 20 per cent gave some reason of this kind. Six individuals stated that they lost courage to perform the test. This small number would indicate that among those who obtained the kits, phobia was a negligible factor (Table 7).

TABLE 7 REASONS FOR NOT USING THE KITS AMONG 1811 INDIVIDUALS

Reason	No. Persons	Per Cent
Lost interest	485	41
Procrastinated	340	29
Had mechanical or other hindrances	242	20
Had recent test	75	
Threw kit away	20	10
Gave kit away	13	
Lost courage	6	
Totals	1811	100

Among the 1730 persons who self-tested, approximately 75 per cent reported no difficulty in performing the test strictly according to instructions; 8.2 per cent admitted having difficulties, mainly in respect to recognizing the color, following the instructions or interpreting the results; and 16.9 per cent experienced no difficulty but admitted they did not follow the explicit instructions, particularly in regard to the time of collection of urine in relation to their meals (Table 8).

TABLE 8 DIFFICULTIES NOTED BY 141 SELF-TESTERS

Difficulties Encountered	Number
Determination of color	70
Following instructions	30
Interpretation of results	16
Performance of test	6
Use of equipment	4
Color and interpretation of results	4
Collection of urine sample	2
Instructions and color	2
Instructions and collection of sample	2
Equipment and determination of color	1
Performance of test and use of equipment	1
Interpretation of results and performance of test	1
Color, performance of test and use of equipment	1
Instructions and performance of test	1
Total	141

Of the group of 3252 studied, 242, as shown in Table 7, did not do the test because of mechanical or

other hindrances, and 141, as shown in Table 8, actually experienced technical difficulties in the performance of the test. The total number having difficulty of some kind was greater than 10 per cent. Therefore, the question of technical difficulties cannot be considered a negligible factor in the failure of the population to use such self-test procedures successfully.

At least four factors influencing the success of a self-testing program seem to stand out significantly in this study. The first is the loss of interest by the participants; the second is procrastination in performing the test; the third is inaccurate interpretation of the test; and the fourth is the failure of the majority of those with suspicious results to seek medical advice.

DISCUSSION

Few attempts have been made to approach any important health problem by distributing equipment and instructions *en masse* for carrying out in the home the technical procedures for diagnosing disease. Therefore, this study in Gloucester, Massachusetts, represented a new departure, the prime purpose of which was to ascertain whether or not a sample of the American population is ready to accept such material, to carry out the procedure and then to take necessary further steps in the direction of medical care. This is a question of basic importance, not only in the field of detection of diabetes but in other fields of preventive medicine and health protection. For example, in time of national emergency it might be desirable to distribute technical equipment and information with instructions to large groups of the population. Such a distribution might have importance in the field of nutrition and nursing as well as in the care of injuries in such an emergency.

An important need exists for early diagnosis of diabetes in order that the patient may be brought under prompt continuous medical care. The great bulk of diabetic patients develop the disease in middle life, and the condition then often exists for many months or even years without the patients' suffering marked and recognized symptoms. Lack of control of diabetes during this period may leave serious sequelae in the retinae and the cardiovascular-renal system, many of which might have been prevented or postponed had the patient received adequate medical care and in particular adequate instruction in the care of the skin and the feet, and the proper use of diet and insulin.

The interest of the public in this field has tremendously increased during the last 25 years. Indeed, in Gloucester the fact that every test kit was picked up within 4 days after the announcement date confirms this impression.

The fact that of the group with positive or suspicious findings only 23.5 per cent sought medical advice seems discouraging. However, certain facts must be taken into consideration not only in interpreting these results, but in attempting to draw conclusions which might be of value to others who may consider similar studies. In the first place the distribution of this technical equipment was not accompanied by any personal advice as might have been accomplished if the distribution had been in the hands of family physicians. Obviously a distribution by family physicians would not have satisfied the objectives of this particular study, which were intended to ascertain the responsiveness of the general public to a program without such personal influence. However, in order to secure the widest possible distribution and highest rate of performance of the test in future distributions of equipment for a medical study, great advantage might accrue if the distribution were made through family physicians as well as through public facilities. The physician might answer questions at the time of the distribution which would aid the recipients in securing better understanding. Another factor probably affecting both distribution and use of the self-testing kit was that of lack of cost. It seems logical to contend that an article which has a purchase price will be more slowly distributed than if it were free. Contrariwise, a purchased article would more likely be used.

A third of the 98 patients whose tests really were suspicious interpreted the results as "no disease" or "no sugar." Twenty-two per cent simply reported that they interpreted the result as meaning that they might have diabetes. Twenty-three of the 98 patients consulted their physicians. The implications of such results make clear that a great increase in efforts to disseminate health information to the public is needed. Although the information should be distributed in such a manner as not to arouse needless fears, it should be expressed in terms that will bring the problem home to the individual.

This study indicates the existence of a wide community interest in any attempt to prevent health disorders by early detection. New methods must be developed which will be more effective. The active participation of all physicians as well as of all public health and educational agencies is necessary in any community program which has for its objective a wide and well-planned health education program which will bring under prompt and continued medical supervision all patients discovered to have diabetes.

SUMMARY

1. The results of a study designed to evaluate the self-testing method of discovering glycosuria in a diabetes detection program have been presented.

2. With adequate community organization providing advance publicity, good acceptance of the program by the public was obtained.

3. An analysis of follow-up studies on 2911 individuals who had obtained self-test kits revealed that 59 per cent performed the self-test and that 41 per cent failed to use the equipment. A comparison of these two groups revealed reasons for performance and non-performance.

4. The majority of those who did not test their urine either lost interest in the project or procrastinated in carrying out the procedure.

5. Among those who performed the test there was found more fear of the disease and a close association with diabetes in family, among friends, or in spouse's family.

6. In the group which performed self-tests, 88 per cent had negative results, 5.6 per cent had positive results, and 6.2 per cent had undetermined results (single green tests).

7. Only 24 per cent of those with positive results interpreted these findings as indicating a need for medical advice, while 36 per cent of the positive group believed that their positive tests indicated that they had no disease or no sugar in their blood or urine.

8. Of those with positive results, 76 per cent failed to obtain medical advice.

9. To obtain a high degree of performance of even as simple a test as the test for glycosuria, maximal cooperation, including participation, of all physicians as well as all public health agencies is desirable.

REFERENCES

[1] Wilkerson, H. L. C., and Krall, L. P.: Diabetes in a New England town, J.A.M.A. *135*:209-16, September 27, 1947.

[2] Joslin, E. P., Root, H., White, P., Marble, A., and Bailey, C.: Treatment of Diabetes Mellitus. 8th ed. Philadelphia, Lea and Febiger, 1946.

[3] Beaser, Samuel B.: The clinical characteristics of early diabetes mellitus. New England J. Med. *239*:765-69, November 12, 1948.

[4] Harting, Donald, and Glenn, Barbara: A comparison of blood-sugar and urine-sugar determinations for the detection of diabetes. New England J. Med. *245*:48-54, July 12, 1951.

ACETONE IN THE BREATH

REFERENCES (Continued)

Bornstein, J., and Lawrence, R. D.: Plasma insulin in human diabetes mellitus. Brit. M. J. *4747*:1541-43, Dec. 29, 1951. (b)

Cadle, R. D., Rolston, M., and Magill, P. L.: Cold-surface collection of volatile atmospheric contaminants. Anal. Chem. *23*:475-77, 1951.

Deuel, H. J. Jr., and Gulick, M.: Studies on ketosis. I. The sexual variation in starvation ketosis. J. Biol. Chem. *96*:25-34, 1932.

Frerichs, F. T.: Ueber den plotzlichen Tod und uber das Coma bei Diabetes (diabetische Intoxication). Ztschr. f. Klin. Med. *6*:1-53, 1883.

Graham, R. L., Harkness, A. L., and Thode, H. G.: An a.c.-operated mass spectrometer for isotope abundance measurements. J. Sci. Instr. *24*:119-28, 1947.

Greenberg, L. A., and Lester, D.: A micromethod for the determination of acetone and ketone bodies. J. Biol. Chem. *154*:177-89, 1944.

Himsworth, H. P., and Kerr, R. B.: Insulin-sensitive and insulin-insensitive types of diabetes mellitus. Clin. Sc. *4*:119-52, 1947.

Hinkle, L. E. Jr., Conger, G. B., and Wolf, S.: Studies on diabetes mellitus: The relation of stressful life situations to the concentration of ketone bodies in the blood of diabetic and nondiabetic humans. J. Clin. Invest. *29*:754-69, 1950.

Hubbard, R. S.: Determination of acetone in expired air. J. Biol. Chem. *43*:57-65, 1920.

Mueller, J.: Ueber die Ausscheidungsstatten des Acetons und die Bestimmung desselben in der Athemluft und den Hautausdunstungen des Menschen. Arch. f. exp. Path. und Pharm. *40*:351-62, 1898.

Price, T. D., and Rittenberg, D.: The metabolism of acetone. I. Gross aspects of catabolism and excretion. J. Biol. Chem. *185*:449-59, 1950.

Somogyi, M.: Effects of glucose feeding upon the ketonemia in healthy man. J. Biol. Chem. *145*:575-79, 1942.

Weichselbaum, T. E., and Somogyi, M.: A method for the determination of small amounts of ketone bodies. J. Biol. Chem. *140*:5-20, 1941.

Widmark, E. M. P.: Studies in the acetone concentration in blood, urine and alveolar air. III. The elimination of acetone through the lungs. Biochem. J. *14*:379-94, 1920

Wrenshall, G. A., Bogoch, A., and Ritchie, R. C.: Extractable insulin of pancreas: Correlation with pathological and clinical findings in diabetic and nondiabetic cases. Diabetes *1*:87-107, March-April 1952.

Temporary Insulin Resistance

REPORT OF A CASE REQUIRING 5490 UNITS OF INSULIN IN 24 HOURS

Joseph H. Crampton, M.D.
*and Clarence D. Davis, M.D.**
THE MASON CLINIC, SEATTLE, WASHINGTON

The administration of 5490 units of insulin in 24 hours has rarely been exceeded. Seventeen patients have been previously cited in the literature as receiving more than 2000 but less than 5000 units,[1-16] six between 5000 and 10,000 units,[17-22] and five more than 10,000 units of insulin in a similar interval. Of these, only nine received more insulin than the patient reported below.

Shepard[26] reported the largest amount of insulin administered. Within a 26-hour period he gave 56,080 units to a patient who was usually treated successfully with 26 units of protamine zinc insulin and 16 units of crystalline insulin; the period of insulin resistance was apparently precipitated by a cold. Arrick[23] gave 21,600 units of insulin in 18 hours after a pelvic operation to a patient who had been treated preoperatively with 1040 units before each meal with little or no effect. Boulin[24] used 19,100 units in 24 hours; one wonders about the potency of this insulin, particularly in view of the fact that the patient was apparently found to be quite insulin-sensitive following the acute episode. Mitrani[25] reported the use of 14,460 units of crystalline insulin in 15 hours in a case of diabetic coma and adnexitis, and 19,440 units in 22 hours in the case of an 8-year-old child with diabetic coma and bronchopneumonia. Davidson and Eddleman[18] administered 9600 units in 17 hours in a case of diabetic coma, but despite this the condition progressed. Autopsy revealed carcinoma of the pancreas with liver metastases. Sindoni[21] recently reported treatment of diabetic coma in a 12-year-old child with 7770 units of crystalline insulin in 24 hours. Berry and Helwig[17] gave 5820 units of insulin in 24 hours to a patient who died 15 days later; necropsy revealed cirrhosis of the liver and acute hemorrhagic pancreatitis. In a case reported by Lozinski and Frohlich[19] 5780 units of insulin were used within 24 hours during an acute infection; no other reason for insulin resistance was determined despite studies for the presence of insulin antagonists in the serum.

*Present address: Division of Endocrinology and Department of Obstetrics and Gynecology, Duke University, Durham, North Carolina.

CASE REPORT

A Belgian-born laborer, 51 years of age, was first seen in the Mason Clinic on March 24, 1947. About 4 months previously there began a rapid loss of weight, associated with polyuria and polydypsia. The weight loss amounted to 15 pounds when the patient came to the clinic. Glycosuria was discovered 3 months prior to admission. He was treated daily with a mixture of 24 units of crystalline insulin and 12 units of protamine zinc insulin. The symptoms subsided and he gained weight temporarily. One month prior to admission he again began to lose weight, at the same time that he was suffering from an upper respiratory infection. He was admitted to the Virginia Mason Hospital primarily for diabetic regulation.

Except for the evidence of recent reduction in weight from 150 to 131 pounds, the patient appeared well. Pigmented exfoliative dermatitis affecting both legs was noted. There was no lymphadenopathy and the thyroid gland was not enlarged. The heart and lungs were normal. The liver edge was not palpable. Arterial pulsations in the extremities were normal.

The urine contained sugar graded 3 plus and albumin graded 1 plus; the diacetic acid test was positive. The hemoglobin was 16.2 gm., the erythrocyte count was 5,900,000, the leukocyte count 6,620 with normal differential. The blood Kolmer and Kahn reactions were negative. The blood sugar was 406, non-protein nitrogen 40, and total serum protein 5.0 with normal albumin-globulin ratio. The thymol flocculation was reported as 3 units, and the bromsulfalein test (5 mg. per kg.) showed less than 5 per cent dye retention in 45 minutes. The basic metabolic rate was minus 8. Roentgenographic studies of the chest, upper gastrointestinal tract, colon, and gall bladder were normal.

He was placed on a weighed diet of carbohydrate 175 gm., protein 90 gm., and fat 90 gm. The daily insulin dosage was increased to 96 units (Figure 1—protamine zinc insulin, unless otherwise stated). The

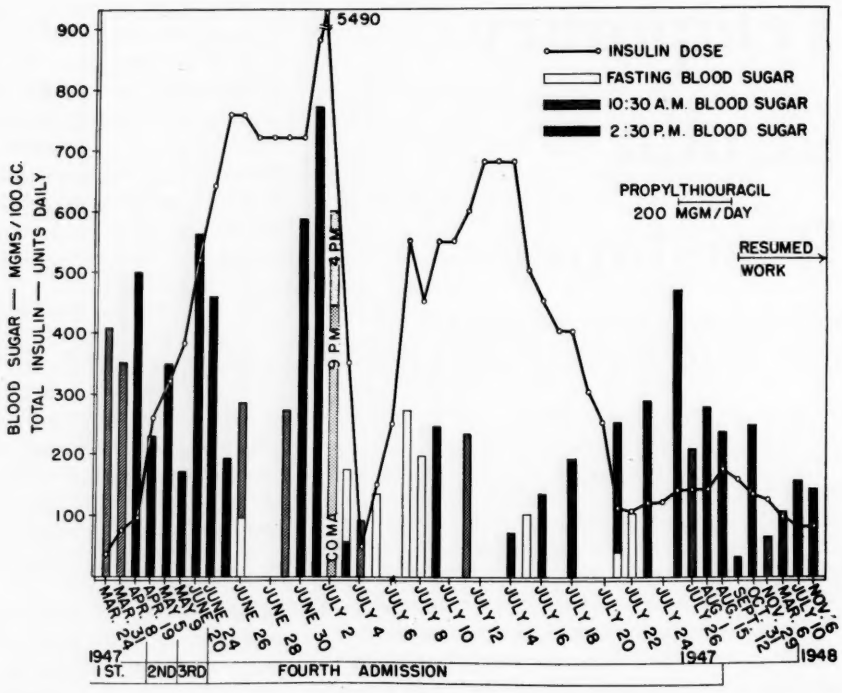


FIGURE 1 Composite graph showing relationship of blood sugar level and insulin dose during the various hospital admissions and part of the follow-up

blood sugar fell from 406 to 349, but he continued to excrete a large amount of sugar in the urine—150-180 gm. in 24 hours.

Towards the end of April the dosage of insulin was increased to 300 units of insulin daily. Because of failure to gain weight, the diet was changed in May to carbohydrate 200 gm., protein 100 gm., and fat 135 gm. The insulin dosage was now 380 units daily. In early May enlargement of the cervical epitrochlear and axillary lymph nodes was noted, and later that month enlargement of the liver was suspected. In June he developed migratory pains involving several joints.

On June 20 the blood sugar was 598; the urine contained diacetic acid. The daily insulin dosage was increased to 560 units. His weight was now 120 pounds. There was increased pigmentation of the legs, and the skin of the remainder of his body was noted to be somewhat darker in color. The liver edge was felt 8 cm. below the right costal margin. The routine tests of the urine and blood were not significantly altered. The corrected sedimentation rate was 42 mm. per hour (Wintrobe). The uric acid was 3.3, non-protein nitrogen 25.8, serum cholesterol 199, and total serum protein 5.2 with albumin-globulin ratio of 1.4. The bromsulfalein test showed 28 per cent dye retention in 45 minutes. The cephalin flocculation was negative. The electrocardiogram was within normal limits.

On June 24, when he received a total of 640 units of insulin in 24 hours, the blood sugar was 460. For the next 6 days, his diabetes was maintained under fair control with 720 to 760 units of insulin daily. The blood sugar then began to rise. On July 1 it was 760, despite treatment with 880 units of insulin. The following day (Figure 2), he received 240 units of crystalline and 200 units of protamine zinc insulin before breakfast. Nausea and vomiting began at 11 a.m. Diacetic acid was present in the urine. During the next 3 hours he was given 700 units of crystalline insulin subcutaneously and 2000 cc. of physiological saline solution. However, his condition progressed toward diabetic coma. At 4 p.m. the blood sugar was 660, and the carbon dioxide combining power was 15 volumes per cent. Immediately he was given 500 units of crystalline insulin subcutaneously and 400 units intravenously. During the next 5 hours he received 1000 units of insulin subcutaneously and 2000 cc. of 1/6 molar sodium lactate. By 9 p.m., in spite of this intensive therapy, the carbon dioxide combining power fell to 12.5 volumes per cent; the blood sugar was 500. During the next 6 hours 2100 units of insulin, 1000 cc. of plasma, 1000 cc. of 1/6

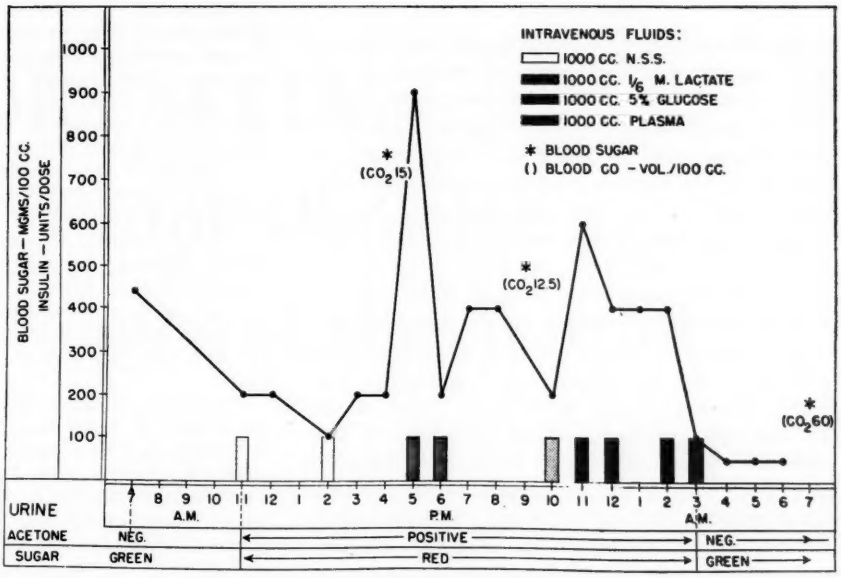


FIGURE 2 Composite graph showing relationship of blood sugar level and insulin dose during the stage of maximum insulin resistance

molar sodium lactate, and 2000 cc. of 5 per cent glucose in physiological saline were administered. At 3 a.m. for the first time since onset of coma, the patient showed clinical improvement, and the urine became free from acetone. Within the next 4 hours he received 150 units of insulin and 1000 cc. of 5 per cent glucose in physiological saline. The carbon dioxide combining power was 60 volumes per cent, and the blood sugar was 176 at 7 a.m. The total insulin administered during this 24-hour period was 5490 units.

The next 3 days were characterized by the maintenance of a satisfactory blood sugar level on a daily lowered insulin requirement, varying from 50 to 350 units. Then during the ensuing 8 days there was a progressive rise in the daily insulin dosage to 680 units. This phase was succeeded by a gradual decline over a period of 12 days to 140 units daily.

A biopsy of the skin was taken from a deeply pigmented area on the left leg. By special stains, hemosiderin was demonstrated throughout the corium and subcutaneous fat. An increase in melanin pigment was shown by hematoxylin and eosin technique.* An enlarged right axillary lymph node, removed for study, revealed no abnormalities.

On July 18, because he continued to lose weight to 115 pounds, his diet was increased to carbohydrate 225 gm., protein 110 gm., and fat 130 gm. This failed to produce gain in weight. One week later, the basal metabolic rate was plus 20. No additional evidence of thyrotoxicosis was noted. Treatment with propylthiouracil, 200 mg. daily, was begun at the end of July and continued for 4 months without incident. There was a gradual fall in insulin requirement. The weight increased to 145 pounds without further addition to the diet. He became able to work satisfactorily as a sawmill laborer.

On November 6, 1948, while on treatment with 80 units of insulin daily, the blood sugar was 145 three hours after breakfast. The liver edge was felt 2 cm. below the right costal margin. The bromsulfalein test showed 4 per cent dye retention in 45 minutes. On May 15, 1950 the fasting blood sugar was 207. He was placed on 24 units of crystalline insulin and 40 units of protamine zinc insulin. A draining sinus appeared in the left fourth rib near the sternum. After two operations, the tuberculous nature of this lesion was established. The area healed following removal of the cartilage.

On March 17, 1951 the patient had a mid-morning blood sugar test of 80, while on treatment with 24 units of crystalline and 32 units of protamine zinc insulin. On July 9, 1951 lumbar pain led to an x-ray of the spine which revealed a compression fracture of the third lumbar vertebra. This was considered to be tuberculous in origin. The patient is now in a sanatorium; his diabetes is under adequate control.

*Dr. Shields Warren, Pathologist at the New England Deaconess Hospital, kindly reviewed these slides. He considered them to show "definite deposits of iron characteristic of hemochromatosis."

DISCUSSION

Insulin resistance of a moderate degree often accompanies the occurrence of acidosis or infection in the diabetic patient. It may also occur with hyperfunction of the thyroid, adrenal, or pituitary glands. Marked insulin resistance may be found in diseases producing severe damage to the liver, such as cirrhosis, hemochromatosis, leukemia, and metastatic carcinoma. Allergy to insulin may be associated with the presence of insulin antibodies which may be demonstrated in the serum of the insulin-resistant patient. In many instances of insulin resistance no obvious cause is demonstrable.

The insulin resistance in our case was first thought to be due to hemochromatosis. This diagnosis was considered established on the basis of the biopsy of the skin and abnormal liver function tests. However, the subsequent course (including the return of the bromsulfalein liver function test to normal) tends to negate this diagnosis. A working diagnosis of hyperthyroidism was next made on the basis of the moderately elevated basal metabolic rate, and the failure to gain weight on a very high caloric intake. None of the other stigmata of hyperthyroidism were present. No marked alteration of his insulin resistance was noted with the administration of propylthiouracil. It now seems unlikely that hyperthyroidism accounted for his insulin resistance.

An infectious process accompanied by liver cell damage is suggested by the arthritic manifestations and subsequent increasing hepatic enlargement, associated with significant diminution in liver function. This, at present, seems to be the most plausible explanation of the insulin resistance demonstrated in this patient.

SUMMARY

The administration of 5490 units of insulin in 24 hours to a patient with acute insulin resistance, probably associated with infection, is reported. The patient is living 4 years and 9 months later with no evidence of insulin resistance despite the development of active tuberculosis in the interim.

REFERENCES

[1] Axelrod, A. R., Lobe, S., Orten, J. M., and Myers, G. B.: Insulin resistance. Ann. Int. Med. 27:555-74, Oct. 1947.

[2] Boulin, Uhry, and Guendot: Cited in Reference No. 24.

[3] Collens, W. S., and Boas, L. C.: The Modern Treatment of Diabetes Mellitus. Springfield, Ill., Charles C. Thomas, 1946, p. 196.

[4] Glass, W. I., Spingarn, C. L., and Pollack, H.: Unusually high insulin requirements in diabetes mellitus: Report of a case. Arch. Int. Med. 70:221-35, Aug. 1942.

[5] Grafe: Cited in Reference No. 24.

[6] Gorman, R. V., Harwood, R., and White, P. D.: Successful treatment of severe diabetic coma complicated by chronic laryngeal obstruction: Report of a case. New England J. Med. *234*:500-03, Apr. 11, 1946.

[7] Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: Treatment of Diabetes Mellitus. 8th Edition. Philadelphia, Lea and Febiger, 1946, p. 379.

[8] Kurnick, N. B., and Scheibel, A. B.: Insulin resistance in diabetic ketosis. J. Mt. Sinai Hosp. *15*:143-49, Sept.-Oct. 1948.

[9] Lawrence, R. D.: Lipodystrophy and hepatomegaly with diabetes, lipaemia and other metabolic disturbances. Lancet *1*:724-31, May 18, 1946.

[10] Levi, J. E., and Friedman, H. T.: Insulin resistance in case of diabetes mellitus and chronic lymphatic leukemia: Report of a case. New England J. Med. *225*:975-78, Dec. 18, 1941.

[11] Lowell, F. C.: Immunologic studies in insulin resistance, measurement of insulin antagonist in serum of insulin resistant patient by blood sugar curve method in mice. J. Clin. Invest. *26*:57-63, Jan. 1947.

[12] Marble, A., Fernald, A. T., and Smith, R. M.: Effect of human diabetic plasma upon blood sugar curves in rabbits following insulin. Endocrinology *26*:735-42, May 1940.

[13] Mason, E. H.: The life history of a diabetic who acquired an unusual tolerance to insulin. J. Clin. Invest. *9*:31, Aug. 1930.

[14] Strouse, M., Martin, H. E., and Lyster, R. W.: Insulin resistance. Tr. A. Am. Physicians *56*:61-66, 1941.

[15] Wayburn, E., and Beckh, W.: Insulin resistance in diabetes mellitus. J. Clin. Endocrinol. *2*:511-18, Aug. 1942.

[16] Wiener, H. J.: Diabetic coma requiring an unprecedented amount of insulin: Report of a case manifesting extreme insulin resistance. Am. J. M. Sc. *196*:211-17, Aug. 1938.

[17] Berry, M. G., and Helwig, F. C.: Marked insulin resistance in diabetes mellitus. Am. J. Med. *4*:923-26, June 1948.

[18] Davidson, J. K., and Eddleman, E. E.: Insulin resistance: Review of the literature and report of a case associated with carcinoma of the pancreas. Arch. Int. Med. *86*:727-43, Nov. 1950.

[19] Lozinski, E., and Frohlich, L. I.: Resistance to insulin. Canad. M. A. J. *46*:62-65, Jan. 1942.

[20] Musimovich, B.: Some observations on insulin resistance. Rev. Asoc. méd. argent. *61*:918, Dec. 15-30, 1947.

[21] Sindoni, Jr., A. M.: An unusual diabetic coma in a child with recovery, with special reference to insulin resistance and hypopotassemia. Am. J. Digest. Dis. *17*:406-08, Dec. 1950.

[22] Smelo, L. S.: Lack of response to insulin: Report of a patient treated with five thousand units per twenty-four hours. South. M. J. *40*:333-40, Apr. 1947.

[23] Arrick, M. S.: Familial insulin resistant diabetes mellitus. J. Clin. Endocrinol. *10*:840, Aug. 1950.

[24] Boulin, R., Uhry, P., Piette, M., and Chauderlot: A case of diabetic coma with insulin resistance treated by the intravenous administration of 19,100 units of insulin. Bull. et mém. Soc. méd. d. hôp. de Paris *63*:598-601, 1947.

[25] Mitrani Russo, S.: A case of insulin resistance. Arch. Hosp. univ. Habana *2*:327-34, Aug. 1950.

[26] Shepard, I. G. H.: A case of diabetes treated with 56,000 units of insulin. Brit. M. J. *1*:576, April 2, 1949.

MORTALITY From Diabetes Throughout the World

CHARACTERISTICS AND TRENDS

Louis I. Dublin, Ph.D.
SECOND VICE-PRESIDENT AND STATISTICIAN
and Herbert H. Marks, A.B.
METROPOLITAN LIFE INSURANCE COMPANY, NEW YORK

INTRODUCTION

The statistics on mortality from diabetes in most countries have been profoundly affected by the new procedure of death certification inaugurated in connection with the Sixth Revision of the International Lists of Diseases and Causes of Death.[1] This procedure came into use in 1949 in some areas and in 1950 in others. In contrast, previous revisions of the International List, which were made at approximately 10-year intervals since 1900, had little effect on the comparability of the statistics of diabetes mortality. While deaths since 1949 or 1950 have been classified for certain series by both the new and the previous procedures, the resulting figures by the latter are only approximate, primarily because the change in certification itself affects the frequency with which diabetes is mentioned. Moreover, physicians and vital statistics offices have not had sufficient experience with the new certificate and procedure to permit accurate evaluation of the effects of the change. This will take a number of years yet and until then, the recent trends in mortality from the disease will remain obscure. For all these reasons, it is necessary to divide the record of diabetes mortality into two parts, with 1949* as the dividing line or, in certain cases, 1950. The major part of this paper will deal with the record for 1948 and prior years.

TREND OF THE DEATH RATE IN THE UNITED STATES

Experience of The Metropolitan Life Insurance Company, 1911-1948

Figure 1 shows the long-term trend in the death rate from diabetes among Industrial policyholders of the Metropolitan Life Insurance Company since 1911, on the basis of the Fifth and earlier revisions of the Inter-

* There was delay in getting the new forms in use in some areas, and for a time many physicians continued to use the old forms. Moreover, many vital statistics offices continued to code and classify causes of death by the Fifth Revision during 1949. This was the practice at the Metropolitan Life Insurance Company also. The statistics for a number of other countries are similarly affected.

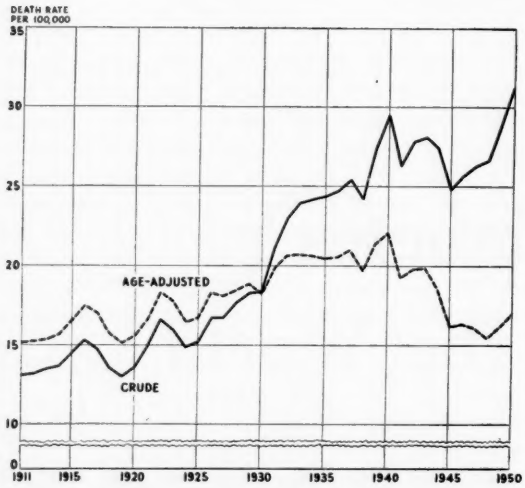


FIGURE 1 Diabetes mellitus: Crude and age-adjusted death rates per 100,000, total persons ages 1 to 74 years. Metropolitan Life Insurance Company, Industrial Department, 1911 to 1950. Age adjustment on basis of Standard Million Population of England and Wales, 1901

national List. Both crude rates and age-adjusted rates are charted. This series is brought up to 1950 but the rates for 1949 and 1950 are subject to the considerations cited in the Introduction. From 1940 to 1948, the crude death rate from the disease tended to fall but it will be noted that 1940 marked the culmination of a long upsweep in the rate, which brought it to a level about double that prevailing in most years prior to 1922. The trend of the age-adjusted or standardized rates makes clear that the shift in age distribution, primarily the steady increase in the proportion of older persons, accounts for most of this long-term rise. In 1940 to 1948 the trend of the age-adjusted rate was markedly downward, and by 1948 the rate had fallen until it was close to the early years of this experience. It is interesting to note, furthermore, that the age-adjusted rates were fairly stable for more than a decade—from 1930 to 1942.

Sex and Color

The trends of diabetes mortality have varied greatly by sex and color. This is summarized in Table 1, which gives both crude and age-adjusted rates in calendar periods from 1920 to 1948. In all groups the long-term trend of the crude rates was upward. The rise was especially great among females, both white and colored. At the peak, the rates for females were about double those in the early years of the experience. Subsequently, the rates fell, but remained well above the initial levels, particularly in females. Changes in the age distribution of the policyholders account for a great part of the rise. Among white males, the age-adjusted rate in this insurance experience fluctuated in a fairly narrow range during the two decades, 1920 to 1944. Among white females, on the other hand, the age-adjusted rate rose with little interruption until 1940. It was then nearly 50 per cent higher than that for the years immediately preceding the inauguration of insulin treatment of diabetes, and for the period 1935-1944, the rate was more than one fourth higher than in 1920-1924. Between 1940 and 1948 the rates adjusted for age fell quite rapidly for each sex. As a result, the death rate for white males in 1945-1948 was about one fifth less than in 1920-1924, and for white females showed a rise of less than 2 per cent.

Among colored males the age-adjusted rate has fallen back in recent years to the level that prevailed 20 years earlier, but among colored females, even with the decline in the rates since 1940, the recent level of the age-adjusted rate is still about 40 per cent above that of the pre-insulin period. This radical change for colored women probably reflects the poor reporting of the disease a generation ago. It is apparent also from Table 1 that at all ages combined the mortality of colored persons in this insurance experience in recent years has not differed materially from that of white persons when allowance is made for differences in age composition of the populations. This represents the situation for the urban wage-earning population.

TABLE 1 Age-adjusted and crude death rates per 100,000 from diabetes mellitus by color and sex at ages 1-74 years. Industrial weekly premium-paying business, Metropolitan Life Insurance Company, 1920-1948

Period	Age-Adjusted*				Crude			
	White		Colored		White		Colored	
	Males	Females	Males	Females	Males	Females	Males	Females
1945-1948	10.5	21.2	10.2	22.5	12.5	36.1	13.3	34.9
1940-1944	13.0	26.4	12.6	27.5	13.4	38.8	15.3	39.9
1935-1939	13.7	27.2	12.3	27.9	12.5	35.0	14.1	37.5
1930-1934	13.8	26.0	12.4	26.8	11.7	29.7	14.0	33.8
1925-1929	13.1	23.0	11.9	21.9	9.9	22.2	11.4	23.6
1920-1924	13.5	20.9	9.0	16.1	10.3	19.6	8.8	17.5

*Adjusted on basis of Standard Million Population of England and Wales, 1901

General Population Experience, 1920 to 1948

In most respects, the trends in the general population between 1920 and 1948 are similar to that in the insurance experience. This is brought out in Table 2. The general population data, however, are distorted somewhat in the war years because persons serving in the armed forces overseas, who were well screened for diabetes, are excluded from the population base used in the computations. Consequently the rates are a little higher for the total population and for males than they would be if corrections were made for this factor.* It may be noted that in recent years the age-adjusted mortality rates for nonwhite males are substantially less than for white males. Among females, however, the rate for nonwhites has come to exceed that among whites.

Trends by Age and Sex

The trends of the death rates from diabetes by age show marked variation both over the short term and the long term. This is brought out in Figure 2, based upon the experience of the Metropolitan Life Insurance Company among white policyholders since 1920. Again limiting the comparison to the period up through 1948, the last decade showed a substantial fall in the rates in virtually all age groups in both sexes. Among males the long-term trend also had been downward at all ages up to 55 and among females at all ages up to 45. At ages beyond these, the trend prior to the last 10 years was upward, particularly among older women. The subsequent shift in the trend at these middle and older ages has been sufficient to wipe out a good deal of the increase during the previous years. Consequently the death rates at the end of the period were below those of the pre-insulin

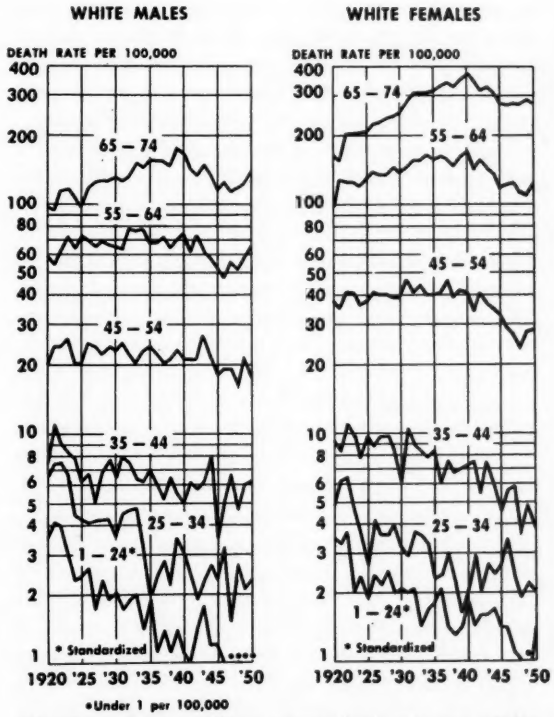


FIGURE 2 Diabetes mellitus: Annual death rates per 100,000 white persons, by sex and age. Ages 1 to 74 years. Metropolitan Life Insurance Company, Industrial Department, 1920-1950

*See paper by I. M. Moriyama,[2] for a graph showing rates for total population, including overseas service personnel.

TABLE 2 Age-adjusted and crude death rates per 100,000 from diabetes mellitus by race and sex. United States, 1920—1948

Year	Age-Adjusted*					Crude†				
	Total	White		Non-White		Total	White		Non-White	
		Male	Female	Male	Female		Male	Female	Male	Female
1948	24.3	19.0	29.2	15.4	31.4	26.4	20.7	34.0	12.3	24.3
1947	24.2	18.8	29.4	14.7	30.4	26.2	20.4	33.8	11.8	23.5
1946	23.0	17.7	28.4	12.4	28.1	24.8	19.3	32.3	10.0	21.5
1945	24.1	18.6	29.6	14.5	28.9	26.6	21.7	33.1	12.3	22.1
1944	24.5	18.7	29.8	15.9	32.4	26.4	21.1	32.9	13.2	24.7
1943	25.8	19.9	31.8	14.8	31.1	27.1	21.5	34.7	12.0	23.6
1942	24.6	19.1	30.3	14.8	29.1	25.4	20.0	32.7	11.9	21.8
1941	25.1	19.1	31.3	13.8	29.3	25.5	19.7	33.3	10.9	21.9
1940	26.5	20.5	32.6	14.9	32.1	26.5	20.9	34.2	11.8	23.7
1935	24.3					22.3	17.9	28.7	10.1	17.0
1930	22.2		Not available			19.1	15.6	24.0	9.4	16.1
1925	20.3					16.8	14.3	20.5	8.7	12.5
1920	19.8					16.1	15.0	18.8	7.2	8.8

Source: National Office of Vital Statistics.

*Adjusted on the basis of the age distribution of the 1940 United States population.
†Estimated mid-year population, excluding armed forces overseas.

years at every age group except after 65 among men and after 55 among women. Notable also is the remarkably low level of recent rates at the younger ages —1 or less per 100,000 at ages 1 to 24 in several years among the males and in one year among the females.

The relative changes in the mortality picture by sex and age are further brought out in Table 3, which gives the rates for the three-year period, 1946-1948, for a decade earlier, 1936-1938, and for the pre-insulin period, 1920-1922, together with the percentage changes between each of the earlier periods and the last period. The magnitude of the changes in this insurance experience is remarkable, with long-term reductions ranging from 40 per cent to 82 per cent in the age groups under 45 and with short-term reductions of 20 per cent or more in several age groups. The larger rate of decline in recent years among females as compared with males in some age groups should be considered in the light of the adverse trend for females in the earlier years.

A notable exception to the general decline in diabetes rates in recent years occurs at ages 25 to 34, where the rates in 1946-1948 were identical with those of a decade earlier. The significance of this is not clear. It may reflect merely the low level of the rates in this age group in recent years. On the other hand, diabetics in this age group have come to include an increased proportion of juvenile cases with long duration of the disease, among whom serious degenerative complications are found with great frequency. Fatalities due to these causes in this group may have been sufficient to counteract the more favorable experience among diabetics of the same ages with recent onset. The fact that the trend described is alike for both men and women gives some weight to this interpretation.

Table 3 serves also to show the characteristics of the age curve for diabetics in each sex as well as the relative mortality of males and females. In both sexes there is a steady rise with advancing age to a peak in later life. Among females this rise is greater than in males after age 45. Consequently there is increasing disparity between the two sexes with regard to the level of the rates after that age. The ratio of the female to the male rate in 1946-1948 rises from nearly 150 per cent at ages 45 to 54, to more than 230 per cent at ages 55 to 64 and also at 65 to 74.

Regional Trends

Recent regional changes in diabetes mortality are presented in Table 4, on the basis of the crude death rates by state for 1939-1941 and 1946-1948. Whereas for the country as a whole the rates in these triennia are virtually identical, those for individual states show changes in varying degree, some of them marked. At the extremes, Montana showed a rise of nearly one third and Oregon a reduction of about one fourth. Of the 48 states and the District of Columbia, 27 showed increases, 21 decreases and 1 no change. In 4 states the decreases exceeded 10 per cent, and in 2 of them 20 per cent. Increases of 10 per cent or more occurred in 7 states, in 2 of them exceeding 20 per cent. The only resemblance to any regional pattern in these changes is a general rise in most of the South and Southwest and a drastic reduction on the Pacific Coast. There are many causes underlying these variations in rate of change of death rates by regions and states. The sharp decline on the Pacific Coast and in some other areas partly reflects the rapid growth of the population of these areas during and after the war, primarily due to migration of young people from other areas. The resulting lower average age of the population would bring down the diabetes rate. An opposite population trend occurred in the South and in certain states in the midwestern farm belt. In turn this would tend to raise the diabetes rates in those areas.

TABLE 3 Death rates per 100,000 from diabetes mellitus. White persons, by sex and age. Metropolitan Life Insurance Company, Industrial weekly premium-paying business. 1946-1948 compared with 1936-1938 and 1920-1922

	Death Rate Per 100,000						Per Cent Change			
	White Males			White Females			White Males		White Females	
Age Period	1946-1948	1936-1938	1920-1922	1946-1948	1936-1938	1920 1922	1946-48 Since 1936-38	1946-48 Since 1920-22	1946-48 Since 1936-38	1946-48 Since 1920-22
1-74*	10.5	13.3	13.6	21.0	27.1	20.8	—21	—23	—23	+ 1
1-24*	.7	1.2	3.9	1.2	1.6	3.5	—42	—82	—25	—66
25-34	2.5	2.5	7.1	2.6	2.6	5.8	0	—65	0	—55
35-44	5.5	5.9	9.1	5.0	6.8	9.5	— 7	—40	—26	—47
45-54	18.0	21.0	23.0	26.3	41.9	38.0	—14	—22	—37	—31
55-64	51.8	68.2	58.1	119.4	155.9	116.6	—24	—11	—23	+ 2
65-74	118.1	153.5	100.7	275.1	332.6	173.7	—23	+17	—17	+58

*Adjusted on basis of Standard Million Population of England and Wales, 1901.

TABLE 4 Death rates per 100,000 from diabetes mellitus 1946-1948 and 1939-1941 compared. United States by place of residence

Division; State	Average of 1946-48	Average of 1939-41	Per Cent Change
United States	25.8	25.9	— 0.4
New England			
Maine	26.5	30.5	—13.1
New Hampshire	36.1	35.8	+ 0.8
Vermont	30.5	32.0	— 4.7
Massachusetts	35.6	35.5	+ 0.3
Rhode Island	40.9	38.5	+ 6.2
Connecticut	33.7	34.4	— 2.0
Middle Atlantic			
New York	41.5	40.0	+ 3.8
New Jersey	32.7	35.5	— 7.9
Pennsylvania	33.6	35.3	— 4.8
East North Central			
Ohio	29.5	30.4	— 3.0
Indiana	26.1	28.2	— 7.5
Illinois	33.0	31.9	+ 3.4
Michigan	27.0	26.3	+ 2.7
Wisconsin	31.6	29.0	+ 9.0
West North Central			
Minnesota	26.7	25.7	+ 3.9
Iowa	26.9	26.8	+ 0.4
Missouri	24.5	25.3	— 3.2
North Dakota	28.4	23.0	+23.5
South Dakota	24.4	24.9	— 2.0
Nebraska	27.6	26.7	+ 3.4
Kansas	23.6	25.7	— 8.2
South Atlantic			
Delaware	30.2	31.1	— 2.9
Maryland	28.3	31.0	— 8.7
District of Columbia	25.5	26.2	— 2.7
Virginia	19.9	19.5	+ 2.1
West Virginia	19.1	17.3	+10.4
North Carolina	14.6	13.8	+ 5.8
South Carolina	15.8	13.6	+16.2
Georgia	13.9	12.2	+13.9
Florida	19.9	18.3	+ 8.7
East South Central			
Kentucky	16.8	16.7	+ 0.6
Tennessee	14.0	13.4	+ 4.5
Alabama	13.0	12.2	+ 6.6
Mississippi	15.1	13.2	+14.4
West South Central			
Arkansas	11.3	10.5	+ 7.6
Louisiana	16.4	16.6	— 1.2
Oklahoma	16.2	14.8	+ 9.5
Texas	14.3	13.5	+ 5.9
Mountain			
Montana	26.1	19.9	+31.2
Idaho	19.1	19.1	0
Wyoming	15.6	16.1	— 3.1
Colorado	19.3	17.0	+13.5
New Mexico	9.8	9.0	+ 8.9
Arizona	11.6	12.1	— 4.1
Utah	17.3	18.7	— 7.5
Nevada	17.1	17.3	— 1.2
Pacific			
Washington	20.3	25.7	—21.0
Oregon	18.5	24.6	—24.8
California	20.7	24.0	—13.8

Source: National Office of Vital Statistics.

These statistics by states show that uniformly the Northeastern states have the highest rates and those in the South and Southwest the lowest rates. In part these variations reflect differences in the age and sex distribution of the population, but social and economic factors as well as the availability of medical facilities are also important influences on the level of the rates.

Death Rates in Large Cities

For this purpose the cities with 500,000 population or more in 1940 have been selected, and trend comparisons have been made on the basis of the changes from 1920 and 1939-1940 to 1948 (see Table 5). It should be noted that the statistics for 1920 relate to deaths occurring in these cities, whereas the statistics for the other years cover all residents of these cities dying within the continental United States. It will be seen that the short-term trend is rather mixed: 6 of these 14 large cities showed gains between 1939-1940 and 1948 ranging from 4 per cent to more than 20 per cent; 5 showed virtually no change and 3 showed declines ranging from 7 to 15 per cent. The long-term trend however, in these cities has been uniformly upward. In fact, in all but 3 cities the 1948 rates are about double

TABLE 5 Death rates per 100,000 from diabetes mellitus in cities of the United States with a population in 1940 of 500,000 or over. 1948 compared with 1939-1940 and 1920

City	Death Rate			Per Cent change 1948 since	
	1948	1939-40	1920	1939-40	1920
New York	48.2	40.7	23.4	+18	+106
Buffalo	43.8	44.5	23.5	— 2	+ 86
Milwaukee	40.6	36.5	19.7	+11	+106
Cleveland	39.6	34.6	17.2	+14	+130
Boston	37.6	36.2	24.2	+ 4	+ 55
Philadelphia	36.3	41.9	18.1	—13	+101
Chicago	36.2	35.9	20.4	+ 1	+ 77
Baltimore	35.0	34.8	20.6	+ 1	+ 70
St. Louis	32.4	34.9	16.1	— 7	+101
Pittsburgh	30.0	30.7	18.8	— 2	+ 60
Washington, D. C.	28.4	27.9	15.1	+ 2	+ 88
Los Angeles	28.1	23.7	16.8	+19	+ 67
Detroit	27.9	22.4	13.4	+25	+108
San Francisco	26.5	31.2	21.9	—15	+ 21

Source: National Office of Vital Statistics.

those for 1920. A much smaller increase was recorded for San Francisco. Space does not permit full discussion of the reasons for the differences in the relative rate of change in the diabetes death rates in these cities, particularly over the short term where the variation is considerable, even if the authors could identify them all. Over the long range the increasingly efficient discovery of the disease and the aging of the population are prime factors in most of these cities. The increase in the proportion of older persons has generally been more pronounced in the large cities than elsewhere because most of these cities have grown comparatively little, largely as the result of the migration of young couples with growing families to the suburbs. This trend has favored an increase in the diabetes rate in the cities themselves.

It is interesting to note the relatively wide range of rates in this group of large cities—from 26.5 in San Francisco to 48.2 in New York in 1948—and also that these rates are in general well above the national figure of 26.4. Among other things, this reflects the superior facilities available in urban areas for the detection and treatment of diabetes.

COMPARISON OF DIABETES DEATH RATES FOR VARIOUS COUNTRIES

The recorded mortality from diabetes in different parts of the world shows an extremely wide range.[3, 4] For many countries no data at all are available. This applies primarily to the undeveloped countries, and for many years also to the areas in Eastern Europe under Soviet domination. Table 6 gives the death rates in a large number of countries for 1948, with comparisons for 1938 and 1928. Caution must be exercised in interpreting international variations in the diabetes death rates because the level of mortality from the disease is influenced by a number of factors, such as the age and sex distribution of the population, its occupational composition, the national income, the degree of urbanization, and the quality and amount of medical care available. Morever, there are differences from country to country in practices of reporting causes of death by physicians and in methods of classification of the primary cause by the offices of vital statistics, where more than one condition is stated.[5, 6]

The United States has the highest recorded rate of all countries in the world. Canada's death rate in 1948 was second highest, about one fourth less than that in this country, whereas prior to World War I it had been little more than half the rate in this country. The 1948 rates for Australia and New Zealand were only slightly less. Of the European countries, Denmark and Belgium reported the highest rates. In the Union of South Africa, the only country on that Continent for which statistics are available, the recorded death rate from diabetes among its population of European origin is on a par with that in many parts of western Europe. In Austria and western Germany rates are fairly low, probably

TABLE 6 Death rates per 100,000 from diabetes mellitus in various countries of the world, 1948 compared with 1938 and 1928

Country	Death Rate			Per Cent Change 1948 Since	
	1948	1938	1928	1938	1928
United States	26.4	23.9	23.6	+ 11	+12
Canada	20.3	13.8	11.1	+ 47	+83
Austria	5.6	10.5		— 47	
Belgium	15.9	20.4		— 22	
Denmark	16.6	20.4	13.4	— 19	+24
England and Wales	7.6	11.5	13.1	— 34	(a)
Finland	5.9	8.1		— 27	
France	7.3	10.1(b)		— 28	
Germany	7.7(c)	19.3(d)		(a)	
Bavaria			8.7		
Prussia			15.3		
Italy	6.9	10.5	7.4	— 34	— 7
The Netherlands	7.4	14.5	16.3	— 49	—55
Norway	12.3	9.0	10.2	+ 37	+21
Portugal	5.3	6.1		— 13	
Spain	5.0	10.0	9.3	— 50	—46
Sweden	6.8	10.8	12.6	— 37	—46
Switzerland	11.2	16.2	10.3	— 31	+ 9
Australia	18.8	17.7	12.0	+ 6	+57
New Zealand	20.1	18.8	12.2	+ 7	+68
Costa Rica	2.3(e)				
Dominican Republic	2.4				
Guatemala	.7(f)				
Mexico	3.6(g)	3.4		+ 6	
British Guiana	15.3				
Chile	4.6(e)	4.6(h)		0	
Colombia	2.5				
Uruguay	13.0(e)	4.8		+171	
Venezuela	2.8(i)				
Ceylon	7.0	11.8		— 41	
Cyprus	4.1				
Israel	8.7				
Japan	2.2	4.2	3.5	— 48	—37
Portuguese India	4.1				
Union of South Africa	10.8(e)	13.5	13.5	— 20	—20

(a)Not comparable; (b)1934; (c)German Federal Republic; (d)1936; (e)1947; (f)1943; (g)1945; (h)1937; (i)1946

reflecting the effects of World War II. In general, recorded death rates from diabetes tend to be highest among peoples of western European stock, somewhat lower in eastern and southern Europe, and lowest of all in the Latin American countries and in Asia.

There can be no doubt that genuine differences exist in the level of diabetes mortality and diabetes incidence even after correction for such factors as the differential age and sex composition of populations. Certainly, insofar as diabetes is associated with abundant nutrition, one would expect real and marked differences between the well-nourished—one might say over-nourished—peoples of this and some other western nations, and the peoples of countries where the masses do not get enough to eat. But it is hard to explain the rather substantial differences between many of the European countries which are fairly alike in important respects—their population structure, standards of living, and medical and public health organization. Consequently it would be desirable to have expert investigation of the causes of the reported differences.

Comparison of the death rates in 1948 with those of 10 and 20 years previous shows a variety of trends. Oddly enough, the increases have been usually greatest for countries with the highest rates, as for example the United States, Canada, Australia and New Zealand. For example, in the United States the 1948 rate was 11 per cent higher than a decade earlier and 12 per cent higher than 20 years earlier. For Canada these increases were 47 per cent and 83 per cent respectively. For Denmark, the rate in 1948 was 24 per cent higher than in 1928, although 19 per cent less than in 1938. In part, the upward trend in these countries reflects the increased average age of the populations, the maintenance of high standards of living, and improvement in medical care as well as intensive efforts to detect the disease.

In contrast, large decreases in the death rate from diabetes, which in part at least may be ascribed to deterioration in standards of living and medical care, are found in such countries as Austria, Spain and Japan. In Europe generally however, the limitations on food supplies in the war and postwar periods could be expected to bring down the incidence and mortality from diabetes. In England, The Netherlands and Sweden, the decline in the recorded rates is believed also to reflect changes in certification and classification of causes of death, because these countries had early put into effect the practices that were later adopted for international use in connection with the Sixth Revision of the International List.

Sex-Age Levels

Publication by the World Health Organization of detailed figures on the deaths from diabetes by sex and age for many countries for one or more recent years[3, 7, 8] has made possible the computation and comparison of rates from the disease in this detail (see Table 7). These comparisons are subject to some of the limitations already described, but at least they eliminate the factors of sex and age distribution. Unfortunately, the age groupings are not identical throughout. Space does not permit an exhaustive analysis of the data and only the major features are discussed. The analysis brings out the universality of certain characteristics by sex and age. With few exceptions the death rates from diabetes among females are higher than those for males. In several countries the margin is quite wide, the rate in females being twice as high as in males. Japan is the only major country in which a lower rate is recorded in women than in men.

The death rates in the childhood and early adult ages are quite low everywhere. In few countries are death rates of more than 2 per 1,000 recorded at ages under 25. The rates increase gradually between ages 25 and 45, but after 45 mount rapidly, particularly in women. The death rates are at the maximum in old age. At the younger ages, rates show only minor differences according to sex, but past 55 there is a marked excess in the death rates of women virtually everywhere. In several countries they are double the rates for men.

When comparisons are made of the mortality rates specific for age and sex in the various countries, great differences are noted between them. For example at ages 65 and over, when the rates are at their maximum, we find these extremes even in countries that are in fairly close proximity: among men, the rate in Denmark in 1949 was 130.9 as compared with 37.8 in France and 19.6 in Finland; among women, the rate in Denmark was 184.8 as compared with 54.8 in France and 40.9 in Finland. The levels for England and Wales, Sweden and The Netherlands are not comparable with the others for reasons already pointed out, but are useful in showing the age characteristics of mortality from the disease there, as well as the comparative levels according to sex in the successive age groups.

In view of the numerous reports on the high frequency of diabetes among Jews, the statistics for the Jewish population of Israel are of especial interest because for the first time they are based on a Jewish population, the age and sex composition of which is known accurately. The data, therefore, are in certain

TABLE 7 Diabetes death rates per 100,000 in various countries of the world by sex and age groups

Country; Sex	Year	All Ages	Age Groups						
			Under 15	15-24	25-34	35-44	45-54	55-64	65 & over
United States*	1948								
Males		20.7	.4	1.0	2.6	4.7	16.2	55.6	165.1
Females		34.0	.7	1.5	2.1	4.6	19.5	95.6	262.7
Canada	1948								
Males		16.2	1.1	1.4	2.7	4.6	13.3	40.9	130.6
Females		24.5	.7	1.3	2.5	3.7	15.8	81.9	204.0
Belgium	1945								
Males		14.2	1.0(9)	2.0	3.3	5.6	10.6	31.3	84.6
Females		19.5	.9(8)	4.4	2.2	5.2	12.6	45.0	99.3
Denmark	1949								
Males		16.7	.4(2)	—	2.2(7)	6.2	7.6	38.7	130.9
Females		23.7	.6(3)	2.1(6)	2.5(8)	2.9(9)	6.0	48.1	184.8
England & Wales	1948-49								
Males		5.3	.3	1.1	.9	1.3	3.2	8.6	35.9
Females		10.1	.3	1.1	1.1	1.3	3.8	16.7	59.2
Finland	1948-49								
Males		4.7	3.3	4.4	2.7	2.0	3.8	9.8	19.6
Females		7.2	2.5	4.7	2.1	1.1(7)	3.5	18.7	40.9
France†	1949								
Males		6 8	.7	1.0	1.4	2.3	5.7	16.1	37.8
Females		11.5	.8	1.4	1.5	2.4	5.3	21.0	54.8
German Federal Republic	1949								
Males		6.5	.9	.7	1.5	2.4	3.9	18.0	40.2
Females		9.9	.7	1.3	1.1	1.8	6.0	24.6	62.4
The Netherlands	1948-49								
Males		5.3	.4	.7	.5(7)	1.2	3.7	9.7	50.8
Females		11.5	.3(9)	.4(6)	1.2	.8	5.1	24.9	106.3
Portugal	1949								
Males		4.5	.5(6)	1.5	2.0	2.5	5.4	15.1	37.3
Females		6.0	.2(3)	1.4	1.9	1.2	6.5	17.5	40.6
Switzerland	1949								
Males		7.3	.4(2)	.9(3)	1.4		8.7		57.9
Females		15.4	.9(5)	1.2(4)	1.4		19.0		96.9
Australia	1947								
Males		11.8	.2(2)	1.3(8)	1.2(7)	2.6	9.2	29.6	96.0
Females		23.3	.9(8)	1.8	1.8	3.1	9.8	51.8	183.9
New Zealand	1949								
Males		13.7	—	—	2.3(3)	2.4(3)	9.3(9)	29.6	105.2
Females		26.5	—	3.2(4)	.7(1)	—	6.2(6)	69.9	194.6
Chile	1946								
Males		4.3	.3(3)	.4(2)	.2(1)	2.8(9)	10.0	29.9	47.9
Females		5.4	.2(2)	.6(3)	1.4(6)	1.6(5)	11.9	24.4	69.9
Israel	1949								
Males		7.2	—	—	1.1(1)	1.1(1)	3.5(2)	30.0(8)	136.8
Females		11.1	—	1.2(1)	—	—	8.1(4)	61.5	160.0
Japan	1948								
Males		2.4	.1	.4	1.0	2.2	6.0	12.0	16.1
Females		2.0	.1	.6	1.1	2.0	4.5	9.7	9.5

Country; Sex	Year	All Ages	Under 15	15-24	25-34	35-44	45-54	55-59	60-69	70 and over
Sweden	1946-47									
Males		5.9	1.0	1.1	1.3	1.0	2.9	7.6	19.2	50.3
Females		10.4	.8	1.8	1.8	2.2	3.5	12.1	33.7	79.9

Country; Sex	Year	All Ages	Under 15	15-29	30-39	40-49	50-59	60-69	70 and over
Italy	1948-49								
Males		6 2	.3	.8	1.2	2.7	8.4	33.1	56.8
Females		8.6	.4	.8	1.4	2.7	13.0	42.4	65.3
Norway	1947-48								
Males		8.4	.8(6)	.9(7)	2.6	2.2(9)	8.4	27.0	85.5
Females		15.4	.4(3)	1.5	1.4(7)	3.6	8.5	40.9	151.9

*White persons. †Preliminary.

Notes: 1. All figures, including those for 1949, are based on the Fifth Revision of the International List of Causes of Death.
2. Figures in parentheses give actual number of deaths in age groups for which the rate is based upon less than 10 deaths.

TABLE 8 Deaths and estimated death rates per 100,000 from diabetes mellitus, 1949-51, based upon 10 per cent sample of death certificates* and total figures for 1949 by geographic divisions

Geographic Division	1951		1950		1949		1949 Total	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
United States reporting area	2,528	16.5	2,501	16.6	2,453	16.5	25,089	16.9
New England	218	24.1	206	22.5	196	21.5	2,037	21.8
Middle Atlantic	591	19.2	627	20.5	624	20.7	6,025	20.1
East North Central	623	20.1	638	20.8	622	20.5	7,023	23.3
West North Central	256	17.9	256	17.9	232	16.3	2,427	17.7
South Atlantic	279	12.9	284	14.0	292	14.5	2,694	13.0
East South Central	141	12.0	114	10.0	132	11.7	1,207	10.8
West South Central	180	12.2	162	11.0	170	11.8	1,656	11.6
Mountain	56	10.8	39	8.1	51	11.2	558	11.5
Pacific	184	12.5	175	11.8	134	9.5	1,462	10.2

Source: National Office of Vital Statistics.

*These data are subject to sampling error. The number of deaths reported each month does not always cover the entire United States but is limited by the completeness of the reporting area.

respects more reliable than any heretofore published. However, the population covered is relatively small. It is quite mixed in origin, representing as it does persons from widely scattered countries. In addition, it must be remembered that the country has been a haven even for those with chronic disease because of the immigration policy adopted by the Israeli government. The number of deaths under age 45 is too small to be of much significance. At ages 55 to 64, the rates for both men and women are about of the same order as the higher rates observed elsewhere in the world, as in this country and in western Europe. This holds likewise for males over 65, but the rate for Israeli females in this age group is exceeded in but few countries.

RECENT STATISTICS FOR THE UNITED STATES BASED UPON THE SIXTH REVISION OF THE INTERNATIONAL LIST

During the three years 1949 to 1951,* the recorded death rates from diabetes in the United States, classified according to the new procedure, have been fairly stable. Table 8 gives the provisional figures by regions based upon a 10 per cent sample of the population for those years, together with the final rates for 1949. For the country as a whole the rate was 16.5 per 100,000 in both 1949 and 1951 and 16.6 in 1950. The figures for broad regions of the country show marked variations during this three-year period, but in part this is due to small numbers and to the nature of the sample. It is evident that for the most populous regions with the largest number of deaths from diabetes the death rates have shown the least variation in this three-year period.

*The figures are not entirely reliable, especially in 1949, because of initial difficulties in changing over from the old to the new procedure, and because the new death certificate was not used everywhere, particularly in the early part of the year. See also remarks in the Introduction.

In 1949, the latest year for which final figures are available for the country and the only full year for which the data are classified by the Sixth Revision, the number of deaths ascribed to diabetes was 25,089, corresponding to a rate of 16.9 per 100,000.[9] For 1948 the number of deaths by the Fifth Revision was 38,638, or 26.4 per 100,000.

In 1949, the figures by color and sex were:

Color and Sex	Number of Deaths	Death Rate per 100,000
White male	8,717	13.2
White female	14,158	21.2
Nonwhite male	714	9.3
Nonwhite female	1,500	18.6

Several vital statistics offices have classified deaths for 1949 and later years according to both the Fifth and Sixth Revisions. These studies are subject to the limitations already described but it will be interesting to review some of the results.

For the country as a whole the first year's experience (1949) with the Sixth Revision, based upon a 10 per cent sample of the death certificates, showed that deaths from diabetes classified by its procedure were only 58 per cent of the total by the Fifth Revision. In other words, the total by the Sixth Revision was 42 per cent less than by the Fifth. For 1950 the deaths from diabetes by the Sixth Revision were 56 per cent of the total by the Fifth Revision or 44 per cent less.

Further analysis along these lines by age, sex, and color [10, 11] is shown in Table 9 and by states in Table 10. The latter is based upon a 10 per cent sample of death certificates for the years 1949 and 1950.

It is clear from Table 9 that the effect of the change in procedure is least at ages under 25, somewhat less at ages 25 to 44 and most marked at ages after 45.

TABLE 9 Ratio of number of deaths from diabetes mellitus by Sixth Revision to number by Fifth Revision of International List of Causes of Death, United States, 1949, Metropolitan Life Insurance Company Industrial policyholders, 1951, and New York City, 1949-1950, by age, race and sex

Age Group	United States 1949* Total Persons	Metropolitan Life Insurance Company 1951† Total Persons	White Males	White Females	Colored Males	Colored Females	New York City 1949-1950 Total Persons	White Males	White Females	Colored Males	Colored Females
All Ages	.58	.56	.57	.55	.67	.57	.44	.44	.43	.53	.54
Under 15	.86	.70	1.20	.56	—	—	1.00	1.00	1.00	—	1.00
15 - 24	1.03	1.11	.87	1.33	—	.60	.95	1.00	.83	—	—
25 - 44	.75	.84	.96	.85	.80	.69	.66	.66	.59	.90	.67
45 - 64	.57	.53	.56	.51	.55	.58	.42	.42	.41	.47	.53
65 - 74	.56	.57	.53	.58	.80	.58	.43	.43	.42	.44	.50
75+	.58	.49	.53	.50	1.20	.36	.46	.44	.46	.43	.52

*Based upon a 10 per cent sample of deaths.
†Based upon a 20 per cent sample of death. Excludes infants under age 1.
Figures underlined based upon less than 10 deaths.

Beyond age 45, where the bulk of the deaths from diabetes is concentrated, the effect is fairly uniform. It is about the same in males as in females, regardless of age, but there are substantial differences according to color between the white and nonwhite populations, the ratios of the numbers of deaths by the Sixth Revision to those by the Fifth being significantly lower in white than in nonwhite persons.

The degree of variation by states is very great. Even if one limits the comparison to those states in which the number of deaths in the two-year sample is fairly large, one finds, for example, a ratio as high as 79 per cent for Texas and as low as 39 per cent for California. In general, as Table 10 shows, the ratios are highest for the Southern states and lowest for the populous states in the Northeast.

It will be apparent that the effect of the change in classification will be least in those types of patients in which the direct complications of the disease, such as coma, gangrene and renal disease are most frequent. These are chiefly young diabetics or patients who for various reasons do not obtain the best modern treatment of diabetes, or fail to cooperate in treatment. Apart from this, local differences in certification practice as well as in points of view regarding the relationship of degenerative changes to diabetes are reflected in the death rates from diabetes in each area. Unfortunately, it is impossible to measure these factors. As it is, the designation of these degenerative conditions of the cardiovascular-renal system as the primary cause of death of diabetics accounts for the major part of the difference in the numbers classified by the Sixth as compared with the Fifth Revision. This has been brought out in a number of recent publications.[12, 13, 14]

The National Office of Vital Statistics has published estimated death rates from diabetes classified by the Sixth Revision for the years 1939 to 1948, based upon its studies of comparability of mortality data by the Fifth and Sixth Revisions.[10] These indicate that the crude death rate for 1949 was 10 per cent higher than the previous maximum in the 1940's and about 20 per cent higher than in 1946. These estimated rates for 1939 to 1948 and the actual rate for 1949 are:

Year	Death Rate
1949	16.9
1948	15.1
1947	14.9
1946	14.1
1945	15.1
1944	15.0
1943	15.4
1942	14.5
1941	14.5
1940	15.1
1939	14.5

In our judgment, the application to earlier years of the results of comparability studies based upon 1949 and 1950 death certificates is inaccurate and leads to erroneous conclusions. It is best to recognize frankly that the statistics prior to 1949 are not comparable with those for subsequent years. The mortality statistics for diabetes should in the future be studied separately for the periods before and since the adoption of the Sixth Revision of the International List, with its new certification method.

DISCUSSION

The recent statistics on mortality from diabetes show a high degree of uniformity with respect to only two major characteristics. First, the disease causes more deaths in females than in males, even with allowance for the differences in the age distribution of the two sexes. The

TABLE 10 Death rates per 100,000 from diabetes mellitus in each state of the United States, 1948 and 1949, by Fifth and Sixth Revisions of International List of Causes of Death

States	1949 Death Rate per 100,000 Sixth Revision (Observed)	1949 Death Rate per 100,000 Fifth Revision (Estimated)	Ratio 6th/5th Revision*	1948 Death Rate per 100,000 Fifth Revision
New England				
Maine	19.1	43.4	0.44	27.2
New Hampshire	23.3	34.8	0.67	33.3
Vermont	22.3	34.8	0.64	29.2
Massachusetts	20.2	42.1	0.48	36.7
Rhode Island	38.7	54.5	0.71	45.4
Connecticut	19.3	39.4	0.49	33.7
Middle Atlantic				
New York	19.8	43.0	0.46	43.8
New Jersey	20.9	38.0	0.55	32.8
Pennsylvania	20.2	35.4	0.57	33.9
East N. Central				
Ohio	22.5	34.6	0.65	29.7
Indiana	18.2	30.3	0.60	26.1
Illinois	26.4	42.6	0.62	33.6
Michigan	25.7	45.1	0.57	28.3
Wisconsin	18.9	29.6	0.63†	32.2
West N. Central				
Minnesota	17.0	30.9	0.55	26.4
Iowa	16.3	29.1	0.56	28.3
Missouri	17.7	27.2	0.65	25.4
N. Dakota	18.4	30.2	0.61	29.4
S. Dakota	20.6	30.7	0.67	26.5
Nebraska	18.2	25.6	0.74	29.8
Kansas	19.1	30.3	0.63	22.6
South Atlantic				
Delaware	26.0	29.2	0.89†	38.3
Maryland	18.3	28.6	0.64	30.5
Dist. of Columbia	14.2	20.9	0.68	25.5
Virginia	11.8	21.9	0.54	21.5
W. Virginia	15.5	21.5	0.72	19.6
N. Carolina	10.2	16.2	0.63	14.8
S. Carolina	12.4	18.0	0.69	15.9
Georgia	11.0	15.9	0.69	14.5
Florida	13.3	22.2	0.60	20.8
East S. Central				
Kentucky	12.2	18.5	0.66	16.4
Tennessee	9.0	15.0	0.60	13.8
Alabama	11.0	15.9	0.69	14.1
Mississippi	11.3	16.9	0.67	14.9
West S. Central				
Arkansas	10.6	15.4	0.69	11.9
Louisiana	13.3	20.2	0.66	17.6
Oklahoma	14.2	24.9	0.57	17.3
Texas	10.6	13.4	0.79	14.6
Mountain				
Montana	18.1	50.3	0.36	23.1
Idaho	11.7	45.0	0.26	19.5
Wyoming	11.2	31.1	0.36†	16.5
Colorado	12.7	22.7	0.56	20.0
N. Mexico	6.8	10.1	0.67†	9.6
Arizona	8.8	16.0	0.55	13.9
Utah	10.3	15.1	0.68	18.1
Nevada	14.5	17.5	0.83†	15.2
Pacific				
Washington	14.3	29.2	0.49	19.8
Oregon	12.5	21.6	0.58	16.7
California	8.9	22.8	0.39	21.1

*Based upon 10 per cent sample of 1949-50 deaths.
†Based upon less than 20 deaths.

cumulative experience on diabetes mortality points to the conclusion that this difference in the frequency of the disease according to sex is real. It is noteworthy also that it is fairly well limited to ages after 40. The persistence with which mortality from diabetes in females is found to exceed that of males would indicate the influence of endocrine factors outside the pancreas. The sex differential has persisted even in those countries which deeply felt the impact of World War II. The excess mortality of females from diabetes is greatest in countries which are most favorably situated economically, in fact it has tended to grow rather than diminish in them. The United States is the prime example of this.

The second consistent characteristic of diabetes mortality is the rise with advancing age, although at no age does diabetes cause more than a small fraction of all deaths. It is significant, moreover, that among diabetics dying in middle and later life the causes of death are predominantly arteriosclerotic lesions of the vascular system. This has become increasingly true as modern therapy of the disease has drastically reduced mortality among diabetics from coma and from infections. The death rate from arteriosclerotic conditions is higher, the onset apparently earlier and the course more rapid among diabetics than nondiabetics.

Trends in diabetes mortality in the decade between 1938 and 1948 show a marked divergence between most of the countries of Europe on the one hand and the United States and the countries of the British Commonwealth on the other. The European rates of recent years are uniformly lower than before, in some countries radically so. This may to a real degree represent an actual reduction in frequency of the disease there because the people of these countries have had to tighten their belts. This would affect not only the incidence of new cases but the longevity of previously known diabetics who have been virtually forced to adhere more closely to a good diabetic regimen. However, this cannot entirely explain the trend. It is certain that the change in pattern of medical certification of causes of death

has played a role in the decline in diabetes mortality in some areas at least. The procedure which the English adopted and which subsequently was embodied in the Sixth Revision of the International List had some influence on those of other European countries, and brought a drop in the recorded death rates. In some European countries, moreover, the reduction may to a degree reflect the impairment of their medical resources, both in personnel and facilities.

Unfortunately, the facts on which one can judge the significance of these sharp declines in diabetes death rates in Europe are not available. Nevertheless, there is ground for the belief that the trend of diabetes mortality there affords a practical demonstration of diabetes control on a large scale by enforced dietary restriction.

In contrast, countries which have experienced an increase or little change in diabetes mortality, such as the United States, Canada, Australia and New Zealand, have enjoyed an abundance of food, so that in part at least their death rates reflect high living standards and high food intake. At the same time, the search for diabetes has probably been most intensive in these countries, partly because of their abundant medical resources and the increased use of laboratory tests in clinical and hospital practice. In addition, the discovery of undiagnosed cases in this country has been stimulated in recent years by the Diabetes Detection Drive of the American Diabetes Association.

To a high degree, the varying levels of diabetes mortality from country to country likewise represent the influence of the factors described. Real differences in incidence and prevalence of diabetes exist, because of genetic and environmental differences between the populations of countries, but in part these differences merely represent the varying adequacy of detection and treatment of the disease.

The achievements of modern treatment of diabetes is clearly reflected in mortality statistics by the long-term decline in the death rate at the childhood and young adult ages. The drastic reduction in diabetes mortality in this period of life and the very low level of these rates today show effectively the boon which insulin brought to the young diabetic.

The recorded increase in diabetes mortality in this country at the older ages, particularly in women, which culminated about 1940, is believed to reflect an actual increase in the prevalence of the disease, but perhaps even more the discovery of increasingly large numbers of mild cases, hitherto overlooked. The reversal of this mortality trend after 1940 is to some extent at least the result of improved treatment of diabetic patients and consequent better control of their disease.

The adoption of a new form of medical certification in connection with the Sixth Revision of the International List aims to increase the uniformity of practices in this regard throughout the world. However, this is an ideal which is not likely to be realized for a long time. The detail in which morbid conditions are reported on the death certificate and the way in which this detail is evaluated in the minds of physicians will continue to vary. Beyond that, the quantity and quality of medical care will remain as factors in the accurate diagnosis of disease. This is of particular importance for a condition like diabetes. Furthermore, even when diabetes is known to exist the certification of it as a primary or a secondary cause represents not merely an opinion but often a point of view, and different physicians frequently will not agree on this matter in individual cases. Actually, the great majority of deaths of diabetics, whether ascribed to the disease or not, are due to or associated with degenerative complications. Consequently, while it has been stated that the death rates from diabetes on the new basis afford an estimate of the risk of dying *from* the disease rather than *with* it, this statement is seriously open to question. One thing is certain. The statistics from diabetes mortality no longer provide a good index to the known or the estimated prevalence of the disease. For that reason, dependable new data of this kind can only be provided by health surveys or other sources of morbidity statistics.

SUMMARY

1. The classification procedure inaugurated with the Sixth Revision of the International List of Causes of Death has brought a sharp reduction in the *recorded* mortality from diabetes in the United States and many other countries. Except as noted, the statistics presented relate to the classification by the Fifth Revision.

2. The long-term trend of diabetes mortality in the United States has been upward, but a major part of this rise has been due to the aging of the population. The age-adjusted death rate actually declined from 1940 to 1948.

3. At the childhood and early adult ages death rates from diabetes have steadily fallen in the United States since insulin came into use. The rates at older ages showed a marked rise, particularly among females, until about 1940 but have declined considerably since then.

4. Death rates from the disease by states are generally lowest in the South and Southwest and highest in the North.

5. Trends of the rates by states and in the large cities of the country between 1938 and 1948 show marked variation.

6. The death rates from diabetes in the various countries of the world have a relatively wide range. The rate is highest of all in the United States and next highest in some other English-speaking countries. The rates are much lower in eastern and southern Europe, in Central and South America and in Asia, and lowest of all in the undeveloped countries. The variation in rates is due in part to differing practices in medical certification of causes of death and in the evaluation of the facts reported. The true situation is not known.

7. Postwar rates in Europe are generally much lower than prewar rates.

8. The statistics by sex and age, presented for a number of countries, show almost uniformly a higher mortality in females than in males, and without exception a rise in mortality with age.

9. The death rates during 1949-1951 in the United States, based upon the Sixth Revision, have been fairly stable for the country as a whole.

10. The effect of the revised procedure varies by age, race and region, but is greatest at the middle and later ages when diabetes is most prevalent.

REFERENCES

[1] Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Sixth Revision of the International Lists of Diseases and Causes of Death. Geneva, Switzerland, World Health Organization, 1948, Volume 1.

[2] Moriyama, I. M.: Is diabetes mortality increasing? Pub. Health Rep. 63:1334-39, October 8, 1948.

[3] United Nations: Demographic Yearbook 1951. New York Statistical Office of the United Nations, 1951.

[4] World Health Organization: Annual Epidemiological and Vital Statistics, 1939-1946. Part I, Vital Statistics and Causes of Death. Geneva, Switzerland, 1951.

[5] United States Bureau of the Census: Classification of Joint Causes of Death. Vital Statistics—Special Reports 5, No. 47, August 30, 1938.

[6] World Health Organization: Interim Commission, Sixth Decennial Revision of the International Lists of Diseases and Causes of Death. International Conference, Problem of Joint Causes of Death, Final Report of the U.S. Committee on Joint Causes of Death, March 30, 1948.

[7] World Health Organization: Epidemiological and Vital Statistics Report *III*, No. 11, November 1950.

[8] World Health Organization: Epidemiological and Vital Statistics Report *IV*, Nos. 5-6, May-June 1951.

[9] National Office of Vital Statistics: Deaths and Crude Death Rates for Each Cause, by Race and Sex, United States, 1949. Vital Statistics—Special Reports 36, No. 13, February 28, 1952.

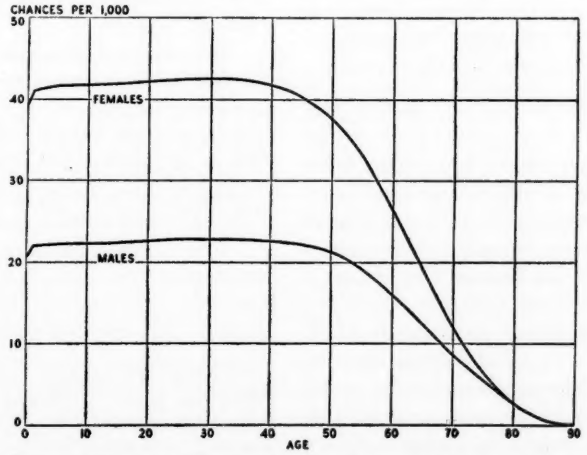
[10] National Office of Vital Statistics: The Effect of the Sixth Revision of the International Lists of Diseases and Causes of Death upon Comparability of Mortality Trends. Vital Statistics—Special Reports 36, No. 10, December 3, 1951.

[11] Unpublished data furnished by C. L. Erhardt, Director, Bureau of Records and Statistics, Department of Health, New York, N. Y.

[12] Marks, H. H.: Diabetes and the Revised International List of Causes of Death. Proc. Am. Diabetes A. 9:347-61, 1949.

[13] Erhardt, C. L., and Weiner, L.: Changes in mortality statistics through the use of the new international statistical classification. Am. J. Pub. Health 40:6-16, January 1950.

[14] Iowa State Department of Health, Division of Vital Statistics: Supplement to Morbidity Report for the Week Ending September 24, 1951.



Chances per 1,000 of eventually becoming diabetic, according to age and sex.

—from *The Facts of Life from Birth to Death*, by Louis I. Dublin, Ph.D. Copyright 1951 by The Macmillan Co., New York.

ABSTRACTS

ABRAHAMSON, E. M. *(The Jewish Hosp. of Brooklyn, N.Y.):* Hyperinsulinism—a factor in rheumatoid arthritis. Am. J. Digest. Dis. *19:*1-4, January 1952.

The author observed that some cases of rheumatoid arthritis have a type of glucose tolerance curve over a 6-hour period which he considers indicative of hyperinsulinism.

ABRAMS, WILLIAM B.; LEWIS, DANIEL W.; AND BELLET, SAMUEL *(Div. of Cardiology, Philadelphia Gen. Hosp., Univ. of Pennsylvania, and Robinette Foundation):* The effect of acidosis and alkalosis on the plasma potassium concentration and the electrocardiogram of normal and potassium depleted dogs. Am. J. M. Sc. *222:*506-15, November 1951.

Normal and potassium-depleted dogs were made acidotic and alkalotic in short-term experiments by the oral administration of ammonium chloride and sodium bicarbonate solutions respectively. The concentration of plasma potassium concentrations rose in the acidotic animals and fell in the alkalotic animals. A linear inverse relationship was demonstrated between the *p*H values and the potassium concentrations.

In general, increased amplitude of T waves was observed in the acidosis experiments, which were associated with a rise in the plasma potassium concentration. Decrease in the amplitude of the T waves occurred in the alkalosis experiments, in which the plasma potassium level fell.

The results suggest that such electrocardiographic abnormalities may be due to changes in the plasma potassium concentration, whether these changes are primarily due to an increased or decreased excretion or are secondary to a disturbance in acid-base balance.

ALBRINK, MARGARET J.; PARENTE, LEONARD; AND GELPERIN, ABRAHAM *(New Haven, Conn.):* Results of a diabetes detection drive. Connecticut M. J. *15:*897-99, October 1951.

In a recent diabetes detection drive in the New Haven (Connecticut) area, urinalyses for sugar were done on 1,025 persons, or 0.5 per cent of the population. The best response was obtained when the co-operation of industry was elicited.

Thirty-two individuals were discovered to have a trace or more of sugar in their urine and were referred to their private physicians for further diagnosis. Of the 32, 8 were previously known diabetics, 2 were definitely diagnosed as new diabetics, and 17 were classed as nondiabetic; 5 were lost to follow up. The diagnostic methods used were probably inadequate in 10 instances.

Screening and diagnostic procedures for diabetes are discussed.

ARDUINO, FRANCISCO; AND VIEIRA DA SILVA, M. C. *(Rio de Janeiro):* Clinical trial with NPH 50 insulin. Rev. brasil. med. *8:*232, 1951.

Thirteen cases of diabetes mellitus were treated with NPH insulin. Three were brittle cases never before under satisfactory control. The diet, following Brazilian eating

habits, was distributed as follows: 20 per cent for breakfast, 30 per cent for lunch, 10 per cent at midafternoon meal, 30 per cent for supper, and 10 per cent at bedtime meal. All patients were observed for 8 weeks. In the majority of cases the control elicited by NPH was equal to or better than that obtained under previous treatment with 2:1 mixture of PZI. Only in the 3 brittle cases were hypoglycemic reactions observed, adjustment eventually being made. In general, the final dose of NPH was slightly lower than the dose of PZI and the same as the dose of the 2:1 mixture being used in these patients.

AZERAD, E.; NATAF, E.; AKSEVEN, J.; AND ALAGILLE *(Paris):* Glomerulohyalinosis in diabetics (intercapillary glomerulosclerosis of Kimmelstiel-Wilson): A clinical study. Presse méd. *79:*1654, December 12, 1951.

This is a clinical study of 15 cases of renal glomerulohyalinosis recorded by the authors in the last three years, 7 of them having been shown by necropsy. The renal syndrome was characterized by edema, albuminuria with hematuria microscopically confirmed, cylindruria, arterial hypertension, and marked azotemia. Diabetic retinitis and cataract were part of the syndrome, each being found in 8 of the 15 cases. The diabetes was far from being always mild or controllable. The blood tests were variable: the cholesterol was generally between 200 and 300 mg. per cent, the serum proteins normal or decreased, the lipids normal or increased. The course was progressive, with a tendency toward cardiorenal insufficiency. In this stage, glomerulohyalinosis had become glomerulonephrosclerosis.

BALMAIN, JUDITH H.; AND FOLLEY, S. J. *(Nat. Inst. for Res. in Dairying, Univ. of Reading, England):* Further observations on the in vitro stimulation by insulin of fat synthesis by lactating mammary gland slices. Biochem. J. *49:*663-70, October 1951.

Insulin added in vitro markedly increased $-Q_{O_2}$, acetate and glucose utilization, and especially R.Q. and 'extra CO_2' (carbon dioxide produced in excess of that required for R.Q. = 1) of lactating-rat mammary-gland slices in glucose plus acetate. This is interpreted by the authors as signifying a stimulatory action of insulin on net fat synthesis. Similar but less marked effects were obtained in glucose, but in acetate the tissue was inert to insulin. Rat mammary-gland slices were unresponsive to insulin, both in glucose plus acetate and in glucose, at the end of pregnancy (19 to 20 days) and after two days' weaning at days 20 to 21 of lactation. Lactating-rabbit mammary tissue was similarly responsive to insulin in glucose plus acetate. Insulin had no effect on the metabolism of lactating-mouse mammary gland in glucose alone. In the absence of insulin, the R.Q. of this tissue was lower in glucose plus acetate than in glucose, but the acid production was somewhat depressed, indicating a slight utilization of acetate. In glucose plus acetate the tissue responded to insulin by moderate increases in $-Q_{O_2}$ and acetate uptake and marked increases in R.Q. and 'extra CO_2.' Udder slices from lactating ewes were inert to insulin both in glucose plus acetate and in acetate. Glycerol exerted an effect qualitatively similar to that of insulin, though less marked in regard to the increases in R.Q. and 'extra CO_2,' on the metabolism of lactating-rat mammary tissue, except that the glucose uptake was not increased by glycerol. The effects of glycerol and insulin were not additive. Udder slices from lactating ewes responded to glycerol in acetate alone; but in glucose plus acetate, glycerol exerted a slightly inhibitory effect. It is suggested that the stimulating effect of insulin on fat synthesis by mammary tissue may be due in part to stimulation of the formation of glycerol from glucose. Since mammary tissue can synthesize and secrete glycerides, the supply of glycerol might be a critical, rate-limiting factor in fat synthesis by this tissue. It is equally possible that the insulin effect is related to the utilization of glucose as an energy source for fat synthesis.

BALME, H. WYKEHAM; AND COLE, LESLIE *(Addenbrooke's Hosp., Cambridge, England):* The heredity of hypertension in diabetes mellitus. Quart. J. Med. *20:*335-51, October 1951.

The incidence of heredity as a causal factor in hypertension has been studied in a series of 209 diabetic patients and in a control series of 100 nondiabetic patients, of whom 50 had hypertension and 50 had a normal blood pressure. All the patients were over 30 years of age. When hypertension occurs in diabetics over the age of 40 years, it resembles essential hypertension in its heredity, age incidence, and sex incidence. Diabetics over 30 years old show a considerably higher incidence of hypertension than that found in the general population. The incidence of a hypertensive family history is significantly greater among hypertensive diabetics than among diabetics with a normal blood pressure. A family history of diabetes occurs with about equal frequency in dia-

betics who have hypertension (37 per cent) and in those who have normal blood pressure (32 per cent). A family history of obesity was about twice as frequent in female hypertensive diabetics as among female nonhypertensive diabetics. The fact is emphasized that hypertension and atheroma, although often met with in the same patient, are not parallel conditions.

BARKER, ONER B.; COMMONS, ROBERT R.; AND SHELTON, E. KOST *(Dept. of Med., Univ. of Southern California Sch. of Med., and the Los Angeles County Hosp., Los Angeles):* Sex-linked juvenile diabetes mellitus: A genetic and clinical study of a family. J. Endocrinol. *11*:608-11, June 1951.

A genetic and clinical study was made of a family of 8 persons (3 boys, 3 girls, and their parents) in which diabetes mellitus was present in the 3 male siblings. The diabetes mellitus was probably inherited as a sex-linked recessive characteristic with heterozygous parents. Other genetic characteristics are presented. Considered mathematically, growth retardation and blondness in the same siblings are thought to be inherited as recessive autosomal characteristics with a homozygous mother and a heterozygous father.

BAUMAN, L.; CANDELA, J. L. R.; AND MARTINO, T. *(Madrid, Spain and New York City):* Prolonged regulation of alloxan diabetes in dogs. Ann. Int. Med. *35*:391-96, August 1951.

The response of dogs to injection of alloxan is variable. Some develop diabetes after 65 mg. per kilogram; others are resistant to doses of 125 mg. per kilogram; a third group suffers a transitory insulin deficiency. Carefully regulated alloxan-diabetic dogs can be maintained in perfect health over long periods without developing any evidence of ocular or arterial disease.

BEARN, A. G.; BILLING, B.; AND SHERLOCK, S. *(Postgrad Med. Sch., London):* The effect of insulin on hepatic carbohydrate metabolism and splanchnic blood flows in man. J. Physiol. *114*:5P-6P, June 29, 1951.

By the technic of hepatic vein catheterization in man, it was found that insulin caused an immediate reduction in the output of glucose from the liver. This was followed by an increased output of glucose. Splanchnic blood flow increased about 25 per cent.

BEASER, SAMUEL B. *(Harvard Med. Sch., Abraham Rudy Diabetic Clin., and Beth Israel Hosp., Boston):* A simplified method for the calculation of diabetic diets. Am. J. Digest. Dis. *19*:6-8, January 1952.

A simplified method which utilizes a unit system of construction for the purpose of easy memorizing has been devised for the calculation of diabetic diets. Clinical application of this method has confirmed its convenience and accuracy. The historical and experimental background of the evolution of this modern simplified diabetic diet is discussed.

BENJAMIN, S. *(Washington, D. C.):* Hypoglycemic reactions to insulin. J.A.M.A. *146*:813-14, June 30, 1951.

Hypoglycemia is considered a misleading term for the abnormal reaction of a diabetic to insulin. It is recommended that this term be replaced by insulin reaction, insulin shock, and insulin coma. The principal criteria for diagnosis of these conditions should be clinical observation based on a good knowledge of insulin reactions in general and a specific knowledge of the reactions of the individual patient.

BERNEY, PAUL W. *(Cedar Rapids, Iowa):* Osteoporosis and diabetes mellitus. J. Iowa M. Soc. *42*:10-12, January 1952.

A case of osteoporosis with diabetes is reported, and the literature is summarized. It is believed that the association of these conditions is often due to poor patient cooperation resulting from cerebral damage in long-standing diabetes.

BISCHOFF, FRITZ *(Chemical Lab., Santa Barbara Cottage Res. Inst., Santa Barbara, Cal.):* Non-depot delayed acting insulin. Am. J. Physiol. *168*:37-43, January 1952.

By treatment of regular insulin in concentrated aqueous urea solution under certain well-defined conditions, the insulin molecule is so changed that it produces a delayed action, as measured by fall in blood sugar upon either intravenous or subcutaneous injection. By the subcutaneous route the delayed effect in rabbits is nearly identical to that produced by the depot insulins, NPH insulin and histone insulin, neither of which produces a delayed effect when administered intravenously.

FEILER, ROSEMARIE *(City Hosp., Berlin-Hohengatow):* Clinical experience with combination insulins "Hoechst," with special emphasis on "Komb" Insulin Hoechst. Deutsche med. Wchnschr. *76*:1448-51, November 16, 1951.

"Komb" insulin is characterized by a slow onset of action, which commences 1½ hours following injection and lasts for 10 to 12 hours in cases which are difficult to control. It is assumed that in some suitable cases a single injection might be sufficient for 24 hours. Tolerance to this preparation is reported as good, no local irritation having been noted. "Komb" insulin seems to be especially well suited for the control of diabetics with a tendency toward nocturnal hypoglycemia. "Komb" insulin, having a ratio of 2 parts depot insulin to 1 part old insulin, provided better control of difficult cases than "Di-Insulin" Novo, which has a ratio of 1 part crystalline insulin to 1 part depot insulin.

FOREIGN LETTERS: ITALY: National convention of internal medicine: Diabetes. J.A.M.A. *148*:488, February 9, 1952.

Professor Antognetti, from the University of Genoa, and Professor Travia, from the University of Rome, discussed diabetes. There are about 54,000 diabetics in Italy, and it was estimated that a similar number of persons have the disease without knowing it.

FORSYTH, C. C.; KINNEAR, T. W. G.; AND DUNLOP, D. M. *(Edinburgh, Scotland):* Diet in diabetes. Brit. M. J. *1*:1095-1101, May 19, 1951.

Fifty patients given a "free" diet were studied over a period of five years. Approximately one-half were newly discovered diabetics who had never been treated, and the other half were patients who had been given dietary instructions at some time, but who were making no effort to adhere to them. All were permitted to eat as their appetities dictated except for the omission of table sugar, jam, chocolates, and sweets; these were excluded with the object of avoiding wide fluctuations of carbohydrate intake.

During the period of study the British rationing system allowed all diabetics extra meat, bacon, milk, cheese, and fats. Thus the patients' standard of nutrition was probably higher than that of the general population. There was no increased tendency for those taking a "free" diet to become obese. If the criticism often levelled at the use of "free" diets, that many of the patients become obese, were true, it would constitute a grave objection to this form of treatment. Of those who did become overweight on a "free" diet all gave a history of obesity in the past. The tendency of patients taking a "free" diet to revert to their pre-diabetic weight held not only for those who were previously obese but for the group as a whole. Dietetically controlled patients, on the other hand, tended to remain below their pre-diabetic weight.

Patients who give a history of obesity before the onset of diabetes, even if they are thin by the time they appear for treatment, should be given controlled diets. Those who have never been overweight may be given full diets without much danger of their becoming obese. The type of insulin required and the number and timing of the injections varied. The majority were stabilized on one injection of soluble insulin and one of protamine zinc insulin half an hour before breakfast, and a second dose of soluble insulin half an hour before the evening meal: 40 of the 50 patients required 2 injections a day.

Repeated blood sugar curves were obtained in one-third of cases in an attempt to assess whether the diabetic state was becoming milder or more severe under "free" diet treatment. In general, the results obtained agreed with the trend shown by the comparative insulin requirements, namely, an apparent increase in severity. Opinion is conflicting about the relationship of hyperglycemia to peripheral vascular disease. While the correlation between the development of some of the degenerative complications of diabetes and poor control of the disease is at least suggestive, the authors believe no one has yet produced evidence that hyperglycemia, accompanied by adequate carbohydrate utilization and good clinical control, is responsible for the development of vascular complications. The present survey can make no contribution to the solution of this problem, since five years is too short a period to warrant conclusions.

GERRARD, JOHN *(Birmingham, England):* The blood sugar level in hemolytic disease of the newborn. Arch. Dis. Childhood *26*:272, June 1951.

The author calls attention to certain similarities between the babies of diabetic mothers and infants with hemolytic disease. Speculations are offered regarding possibly

interrelated effects of impaired placental function, maternal pituitary hyperfunction, hexokinase activity in the fetus, islet hyperplasia, diminished cerebral uptake of glucose, kernicterus, interplay between levels of blood sugar, circulating insulin and diabetogenic or growth hormone.

GREIF, STEFAN; AND MORO, E. *(Graz):* Intravenous glucose in diabetic coma. München. med. Wchnschr. 93:2564-67, December 21, 1951.

The authors are in disagreement with the opponents of glucose administration in cases of diabetic coma and are inclined to go along with those who take a middle-of-the-road policy. They do not deem it advisable to make blood sugar at a fixed time (six hours after initiation of treatment, for instance) as an indicator for intravenous glucose. The deciding factor, in their opinion, is the speed of blood sugar decline.

GROTTE, GUNNAR; KNUTSON, ROBERT C.; AND BOLLMAN, JESSE L. *(Mayo Foundation, Univ. of Minnesota, Rochester):* The diffusion of dextrans of different molecular sizes to lymph and urine. J. Lab. & Clin. Med. 38:577-82, October 1951.

Dextrans injected intravenously diffuse from the blood into the lymph and into the urine. In the rat and the dog the concentration in the lymph from the thoracic duct within a few hours after injection is similar to that in the blood. Dextrans of sizes from 24,000 to 205,000 molecular weight enter the lymph and also appear in the urine. The amount excreted in the urine appears to be inversely proportional to the molecular weight. The larger sizes of dextran are retained longer in the blood. Dextran does not appear to be converted to glucose in appreciable amounts in the depancreatized dog.

GRUBER, M. *(Lab. of Physiological Chemistry, Univ. of Utrecht, Netherlands):* Synthesis of fat from carbohydate in thiamin deficiency. Biochim. et biophys. acta 7:480-81, September 1951.

Experiments have not given the slightest indication that thiamin deficiency causes an impairment of the synthesis of fat from carbohydrate.

GRUNBERG, A.; DAVIES, H. L.; AND BLAIR, J. L. *(St. Catherine's Hosp. Birkenhead, England):* Diabetic gangrene. Brit. M. J. 2:1254-57, November 24, 1951.

Gangrene in the diabetic is extremely amenable to conservative surgery, and a radical amputation should never be performed as a routine measure. The theory is advanced that, although control of the infection of the gangrenous tissue is of paramount importance, the diabetic state stimulates the formation of a collateral circulation which is usually well established when the crisis of peripheral vascular thrombosis supervenes.

GURIN, SAMUEL *(Univ. of Pennsylvania):* The biosynthesis of fatty acids and cholesterol and the hormonal control of these processes. Yale J. Biol. & Med. 24:236, December 1951.

The influence of hormones upon synthesis of long-chain fatty acids from radiocarbon-labeled acetate by rat and cat liver slices was described. Insulin increased the synthesis of fatty acids, but it did not reverse the diminished synthesis demonstrated by liver slices of pancreatectomized or alloxan-treated animals. Liver slices of hypophysectomized animals synthesized fatty acids to a greater extent than livers of intact animals. Extirpation of both the pancreas and the hypophysis did not influence the amount of fatty acids formed, but the addition of purified growth hormone to the liver slice of such an animal lowered the fatty acid production. Growth hormone itself was without effect on the yield of fatty acids, although it antagonized the increased synthesis engendered by insulin. There was no quantitative difference between the production of fatty acids from acetate by normal livers and production by livers of pancreatectomized and adrenalectomized cats. Addition of cortisone lowered fat synthesis.

It is possible that in diabetic states, conversion of two carbon fragments to fatty acids is blocked and an alternative metabolic pathway is taken, leading to the formation of excess ketone bodies and cholesterol.

GUY, WILLIAM B. *(Univ. of Pittsburgh, Sch. of Med., Pittsburgh):* Cutaneous diseases associated with diabetes. Pennsylvania M. J. 54:1052-55, November 1951.

The author believes that generalized pruritus, although traditionally associated with the disease, does not have a direct etiologic connection. His personal experience

fails to reveal a single instance of diabetes uncovered from such a presenting symptom. Pruritus pudendi is another matter. Pruritus vulvae is frequently associated with glycosuria; the logical explanation for this probably is that when a sugary solution dries on the skin, it sets up itching. Furunculosis has a tendency to occur frequently with diabetes as a complication; like all pyogenic infections, it often makes the primary disease harder to control. Whether dermatophytosis, a superficial mycotic infection of the skin, occurs more frequently in diabetics has often been questioned. In fact, interdigital mycotic infections of the feet are so common in nondiabetics that there would have to be practically a 100 per cent incidence in diabetics for them to be of any significance. Monilial infections, caused by the yeast organism *Monilia albicans,* certainly are more often seen in diabetics.

Xanthoma diabeticorum is a distinct clinical entity, of importance to dermatologists because it must be distinguished clinically from xanthoma tuberosum multiplex.

Necrobiosis lipoidica diabeticorum is by no means limited to diabetics. The disease produces no subjective complaints and no treatment used to date is of any avail.

HARDWIG, ROBERT P.; AND SCHROCK, CHRISTIAN E. *(Waverly, Iowa):* Spontaneous hypoglycemia: The use of a provocative insulin test. J. Iowa M. Soc. *42*:6-10, January 1952.

Spontaneous hypoglycemia of the functional type is not uncommonly found in routine office practice. Problems in its recognition are discussed, and a helpful, rapid test for office use which aids in its detection is outlined. A brief review of the differential diagnosis and treatment of the more commonly encountered etiologic types is presented.

HARRIS, H. *(Galton Lab., Univ. Coll., London):* Genetical prognosis in diabetes mellitus. Proc. Roy. Soc. Med. *44*:913-15, November 1951.

Although the predisposition to develop diabetes mellitus is genetically determined, the detailed genetic situation and the environmental conditions determining manifestation of the disease are still obscure. Genetic prognosis must therefore be based on empirical considerations. With the familial distribution derived from a survey of the incidence of the condition among the relatives of a large series of diabetics being used as a standard, approximate prognostic indications are given for certain situations that may arise in practice.

HOKIN, L. E. *(Dept. of Biochemistry, Univ. of Sheffield, England):* Amino-acid requirements of amylase synthesis by pigeon-pancreas slices. Biochem. J. 50:216-20, December 1951.

Of the 16 amino acids found in crystalline *a*-amylase, 10 have been found necessary and also sufficient for maximum synthesis of the enzyme by pigeon-pancreas slices. These amino acids are: tryptophane, arginine, threonine, valine, tyrosine, lysine, leucine, histidine, isoleucine, and phenylalanine. They include every "essential" amino acid present in crystalline *a*-amylase and one "nonessential" amino acid, i.e., tyrosine. In the synthesis of amylase, tryptophane, tyrosine, valine, and leucine can be replaced 80 to 100 per cent by their respective ketonic acids. The origin of the "nonessential" amino acids is discussed. Glutamate plus glutamine comprise about 50 per cent of the total free amino nitrogen of pigeon pancreas. These compounds, by transamination of intermediates of carbohydrate metabolism, may give rise to aspartic acid and alanine.

HOLMES, C. B.; WALSH, G. C.; BAIRD, M. M.; WHITELAW, D. M.; SIMPSON, W. W.; AND MCINTOSH, H. W. *(Vancouver, B. C.):* The effect of cortisone on the nephrotic syndrome occurring in diabetics. Canad. M. A. J. 65:26-29, July 1951 .

Three cases of the nephrotic syndrome occurring in patients with diabetes of long standing have been treated with cortisone. Initially, all 3 cases showed a decreased carbohydrate tolerance, as evidenced by raised blood sugar or increased requirement for insulin. A decreased requirement for insulin occurred after 3 weeks in 1 patient. The possible reasons for this are discussed. Increased proteinuria occurred in all patients.

HORNE, G. O. *(General Infirmary, Leeds, England):* Insulin loss during injection. Lancet 2:1038-39, December 1, 1951.

The author points out the disadvantages of using a tuberculin-type syringe and a smaller-gauge needle in an effort to reduce insulin loss during injection. The

alternative suggestion is to take up a bubble of air in the syringe with the insulin and to inject the hormone so that the residual bubble of air will force the last part of it into the site of injection.

HORNE, G. O. *(Shrewsbury, England):* Correspondence. Lancet *1*:51, January 5, 1952.

The problem of insulin loss during injection is discussed. The author reiterates his suggestion that the injection of a residual air bubble will prevent the loss of the amount of insulin which is usually left in the syringe and needle after injection.

HORSTMANN, P. *(Odense, Denmark):* The oxygen consumption in diabetes mellitus. Acta med. scandinav. *139*:326-30, 1951.

Oxygen consumption in cases of diabetes was reported to be increased an average of 10.3 per cent, independently of sex and age. Subcutaneous injections of insulin caused a transient fall of the oxygen uptake to normal values. This effect lasted only three to four hours.

HORSTMANN, P. *(Odense, Denmark):* Fatal insulin hypoglycemia in a patient with panhypopituitarism. Acta endocrinol. *8*:362-70, 1951.

A 57-year-old woman who had had 2 deliveries, the last one 30 years prior to the admission to hospital, showed clinically marked signs of myxedema, with an oxygen consumption rate of —30 per cent. She was very sensitive to thyroid, small amounts of which brought about life-threatening crises. Following the intravenous injection of 8 International units of insulin, a profound hypoglycemia developed; the patient did not recover in spite of oral and parenteral administration of considerable amounts of beet sugar and glucose. Death ensued ten hours after the insulin injection. An almost total atrophy of the pituitary and suprarenal glands, together with marked atrophic changes in the thyroid glands, was found at autopsy. The case is considered as one of pituitary myxedema, primarily caused by the hypophyseal atrophy. Great caution has to be observed in the use of insulin in such cases, especially if adrenal insufficiency is suspected.

IGERSHEIMER, JOSEPH *(Tufts Coll. Med. Sch. New England Center Hosp., Boston):* Advances in ophthalmology from a general medical standpoint. Bull. New England M. Center *13*:264-68, December 1951.

Diabetic retinopathy relates only to the duration of the general disease, not to the severity of the diabetes, the cholesterol level, or hypertension, and it influences only the prognosis for vision. Some features that look like fine hemorrhages are in reality microaneurysms. These are characteristically round, the larger ones having a bright central reflex, and a few are encircled by a narrow pale halo. Hemorrhages that have no relation to aneurysms are of a more irregular longitudinal shape, and they come and go. Aneurysms remain unchanged for years; occasionally they are converted into a sharply outlined white spot (hyalinized). Differentiation is not always easy although generally it is possible. Aneurysms are also seen in nondiabetic diseases (malignant hypertension and other retinopathies); however, in these they are rare and occur in very small numbers, whereas in diabetes they may be innumerable.

INGLE, D. J.; NEZAMIS, J. E.; AND MORLEY, E. H. *(Upjohn Company, Kalamazoo):* Work output and blood glucose values in severely diabetic rats with and without insulin. Am. J. Physiol. *165*:469-72, May 1, 1951.

The presence of insulin favors pathways of glucose utilization which compete with contracting muscle for the available carbohydrate.

JABLONSKY, A. *(Jeannette, Pa.):* Penicillin ointment as a topical agent in the treatment of infections of the foot and toes, with osteomyelitis, in diabetic patients: Two cases, one with three separate lesions. Am. Pract. & Dig. Treat. *2*:701-07, August 1951.

The effectiveness of penicillin ointment as a topical treatment has been demonstrated in four consecutive instances of infection of the forefoot and toes. Two of the cases were further complicated by the presence of osteomyelitis.

JOHN, H. J. *(Cleveland):* Infection of the gall bladder and diabetes. Am. J. Digest. Dis. *18*:109-22, April 1951.

The relationship between gall-bladder infections and diabetes is an important one, from the standpoint of

their management. Removal of an infected gall bladder often improves the carbohydrate metabolism in such cases, but it does not always insure that this improvement will be permanent. A brief résumé is given of the literature on the relationship of cholecystitis and diabetes.

JONES, H. B.; GOFMAN, J. W.; LINDGREN, F. T.; LYON, T. P.; GRAHAM, D. M.; STRISOWER, B.; AND NICHOLS, A. V. *(Berkeley, Cal.):* Lipoproteins in atherosclerosis. Am. J. Med. *11*:358, September 1951.

Further studies with the ultracentrifuge confirm the original reports that the concentration of S_f 12-20 class of lipoprotein molecules in the serum is significantly higher in patients exhibiting evidence of atherosclerosis. Classes above S_f 20 and below S_f 12 are negatively correlated. Parenteral injection of heparin causes transformations extending over the entire lipoprotein spectrum and shifts lipoprotein transport in the direction of normality.

JOSLIN, ELLIOTT P. *(Boston):* Status of living diabetics with onset under forty years of age. J.A.M.A. *147*:209-13, September 15, 1951.

Diabetics are living longer than ever before. So many of them present distressing complications after years of the disease that this article has been written to show that the condition of some of the author's younger patients after a quarter century of the disease warrants optimism. These 760 patients with diabetes of 25 years' duration or more fall into 4 groups: 1, quarter-century victory-medal diabetics, numbering 23; 2, those with onset in childhood who have survived more than 30 years, numbering 40; 3, those with onset in childhood who have had the disease between 25 and 30 years, numbering 181; and 4, those whose onset was between the ages of 15 and 40 and who have survived 25 years or more, numbering 516. *Medal diabetics are symptomless*—they are free from complications; they have no complaints. They do not even have neuritis. It is hoped that they will not forget they have diabetes, and it is a blessing they must be pricked each day as a reminder they are vulnerable. There is always more worry over the patient who is allowed to give up insulin than over the one who takes it. Details of a few of the individual medal cases are given.

KAY, W. W.; AND THORLEY, A. S. *(Belmont Hosp., Sutton, and Mental Hosps. Group Lab., West Park Hosp., Epsom):* Some biochemical aspects of hypoglycemic coma (II). Proc. Roy. Soc. Med. *44*:973-76, November 1951.

In confusion, light coma, and deep coma, there is a significant accumulation of excess base over acid in the serum as the effect of administered insulin proceeds. These changes in base-acid difference do not appear to be related to insulin dosage or gastric acidity, nor are they accounted for by accumulations of pyruvate or lactate. It is suggested that the extra base is taken up by protein and small increments of acids. Alkalization of patients before administration of insulin has no clear influence on its effects. The effects of small doses of insulin on circulating electrolytes and eosinophils, are similar to those of adrenocortical stimulation.

KEMPE, C. HENRY; SILVER, HENRY K.; SMYTH, FRANCIS SCOTT; GOFMAN, JOHN W.; AND JONES, HARDIN B. *(Div. of Pediatrics, Univ. of California Sch. of Med., San Francisco, and the Donner Lab., Berkeley):* The lipoproteins of serum in infancy and childhood. I. Lipoproteins in normal children. J. Pediat. *40*:11-18, January 1952.

Determinations of the concentration of certain lipoprotein molecules (S_f 10-20 class) are reported for 147 normal children ranging in age from birth to 15 years. These molecules previously were shown to be associated with atherosclerosis.

Similarity of values was found for normal male and female children. Boys had significantly lower values than those previously determined for normal male adults, but the levels for girls approximated the range for young normal female adults.

No correlation was present between the concentrations of these lipoproteins in the serums of newborn infants and their mothers. No significant correlation was noted between the total serum cholesterol and the level of the S_f 10-20 class.

KINSELL, LAURANCE W.; MARGEN, SHELDEN; MICHAELS, GEORGE D.; AND MCCALLIE, DAVID P. *(Univ. of Calif., and U.S. Naval Hosp., Oakland):* Studies in fat metabolism. II. Evaluation of the effect of testosterone propionate upon ketone, carbohydrate, and protein metabolism in a patient with diabetes mellitus complicated by thyrotoxicosis. J. Clin. Investigation *30*:1486-90, December 1951.

A patient with severe diabetes mellitus associated with severe thyrotoxicosis, on a chemically constant dietary intake and constant insulin therapy, manifested a fall in urinary sugar, nitrogen, and ketones of quite marked degree during the administration of 150 mg. of testosterone propionate daily. It is suggested that under these experimental conditions the changes observed may have been due, in part at least, to a direct effect of testosterone upon fat or ketone metabolism.

KOMRAD, E. L.; AND LOEW, E. R. *(Boston Univ. Sch. of Med.):* Inhibition of epinephrine-induced hyperglycemia with adrenergic blocking drugs. Am. J. Physiol. *165*:66-72, April 1, 1951.

A characteristic property of the more potent adrenergic blocking agents is the ability to diminish epinephrine hyperglycemia.

KVAMME, E. *(Asker, Norway):* Acid soluble phosphorus compounds in human blood investigated with radioactive phosphorus: I. The action of insulin and glucose. Scandinav. J. Clin. & Lab. Invest. *3*:140, 1951.

Glucose and insulin had similar effects, increasing the rate of turnover of acid-soluble phosphorus compounds in the blood (especially in the 10-minutes acid-hydrolyzable fraction) at 30 and 60 minutes after the injections, measured by the use of P_{32} as a tracer. Inasmuch as the concentration of inorganic phosphorus in plasma and whole blood did not diminish, the uptake of inorganic phosphorus must be compensated by a corresponding influx from the tissues.

LANDAUER, WALTER *(Univ. of Connecticut):* The effect of insulin on development of duck embryos. J. Exper. Zool. *117*:559-71, August 1951.

As in chicken embryos, injection of insulin into developing ducklings produces abnormalities of tail (rumplessness), extremities (micromelia), and skull (beak defects, buphthalmia), in addition to reduction of body size. The incidence of insulin-induced rumplessness is much lower in ducklings than in chicks; that of micromelia, beak defects, and buphthalmia, on the contrary, is much higher among ducklings. During the first three days of incubation, insulin was less toxic for duck than for chicken embryos, but the reverse was true during subsequent days.

LEEVY, CARROLL M.; FINEBERG, JACOB C.; WHITE, THOMAS J.; AND GNASSI, ANGELO M. *(Jersey City Med. Center, Jersey City, N. J.):* Hyperglycemia and glycosuria in the chronic alcoholic with hepatic insufficiency. Am. J. M. Sc. *223*:88-95, January 1952.

The authors report upon 10 patients with histories of chronic alcoholism and poor dietary habits prior to the appearance of a diabetic syndrome with hyperglycemia and glycosuria in whom hepatic therapy without insulin caused improvement in the hepatic status and disappearance of the hyperglycemia and glycosuria. None of the patients had familial diabetes or evidence of pancreatic, pituitary, adrenal, or thyroid disease to cause a disturbed carbohydrate metabolism.

These therapeutic responses suggested that the liver disease produced hyperglycemia by interfering with hepatic homeostasis of blood sugar in 4 of the patients and by the unmasking of a relative insulin insufficiency in 4 others. In the latter group, hyperglycemia recurred with intercurrent illnesses and developed after minor hepatic changes and disappeared with short-term hepatotherapy, although the basic liver pathology remained. The mechanism was obscure in 2 patients who developed insulin-resistant diabetes.

Significant ketosis was not observed, although patients consumed large quantities of whisky, ate poorly, and received no insulin. None of the patients had clinical evidence of accelerated degenerative vascular disease.

The differential diagnosis of diabetes with secondary liver changes and hepatogenic diabetes is difficult and seems to be most readily made by prolonged therapeutic observation. The latter is suggested by a history of exposure to hepatotoxins or liver injury prior to the appearance of the diabetic syndrome; by evidence of liver disease; by absence of a familial history of diabetes or history or clinical evidence of pancreatic, pituitary, adrenal, or thyroid disease; and by disappearance of hyperglycemia and glycosuria on hepatic therapy without insulin.

Prognosis for both the liver and carbohydrate disturbances is good if proper treatment is given. Relapse resulted on return to alcoholism and poor diet.

LEVINE, RACHMIEL *(Chicago):* Metabolic and endocrine research. Ann. Rep., Med. Res. Inst., Michael Reese Hosp. *22*:11-13, 1950.

One of the major long-term research interests of this laboratory—the mechanism of action of insulin—was pursued actively during the past year. New evidence

was added to support the theory of insulin action, formulated in 1949. It is now reasonably certain that insulin influences the cell membranes of muscles, whereby these cell surfaces become more "permeable" to the sugar of the blood. Consequently, glucose is more readily taken up by the tissues and used by them for fuel and food storage. The metabolic transformations of glucose in the cell interior are independent of the presence or absence of insulin.

LISTER, JOHN; AND MAUDSLEY, ROY H. *(Royal Free Hospital, London):* Charcot joints in diabetic neuropathy. Lancet 2:1110-13, December 15, 1951.

The authors state that neuropathic joint changes are an infrequent complication of diabetic neuropathy. A case in which the tarsus is involved is described. The etiology of the condition remains obscure, but, in addition to the peripheral sensory changes, there was evidence of autonomic involvement in the case described and in several previously reported cases. Until lately, improvement has never been observed, but a recent report suggests that lumbar sympathectomy may arrest the condition. In the present case, amputation was eventually necessary. Mention is made of the fact that diabetic neuropathy may go unrecognized unless the possibility of such a complication is kept in mind.

LONG, C. *(Dept. of Biological Chemistry, Univ. of Aberdeen, Scotland):* Studies involving enzymic phosphorylation. I. The hexokinase activity of rat tissues. Biochem. J. 50:407-15, January 1952.

Homogenates of several rat tissues have been assayed for hexokinase activity, the rate of glucose disappearance in the presence of adenosinetriphosphate being used as a measure of activity. Optimal rates of glucose utilization were obtained when the homogenates were prepared in a potassium phosphate buffer, *p*H 7.8, containing potassium fluoride, and the incubation medium contained the following components (final concentrations in brackets): glucose (0.0012-0.0024 M); potassium adenosinetriphosphate (0.005 M); magnesium chloride (0.005 M); potassium fluoride (0.05 M); potassium phosphate buffer, *p*H 7.8 (0.04 M); potassium chloride (0.042 M). The incubation was conducted in air at 30° and varied from 2 to 6 minutes' duration. Under the above conditions, the amount of glucose utilized was proportional to the volume of homogenate used and in most cases increased linearly with the duration of incubation until at least 80 per cent of the glucose had disappeared. Results showed that brain was the most active tissue and liver the least active. A number of tissues have been considered in the light of the relationship between their hexokinase activities and their physiological functions.

LOURAU, M.; AND LARTIGUE, O. *(Paris):* The existence of a functional relationship between the glycemic level and the speed of absorption of glucose from the intestine. Experientia 7:428-30, November 15, 1951.

There is a functional relationship between the glycemic level and the rate of glucose absorption from the intestine. Over a range of 125 mg. per cent to 1,400 mg. per cent the glucose absorption rates are decreasing as the logarithms of glycemic level. Under our experimental conditions, the glucose absorption rate is zero at the glycemic level of 550 mg. per cent. Above this level, amounts of glucose related to the blood sugar concentration are excreted into the intestinal lumen.

LUNTZ, GEORGE R. W. N. *(Tuberculous Diabetic Unit, Romsley Hill Sanitorium, Halesowen, Worcester, England):* Correspondence. Lancet 2:1144-45, December 15, 1951.

The subject of insulin loss during injection is discussed, with reference to recent articles on the problem.

MACKLER, BRUCE; LICHTENSTEIN, HENRIK; AND GUEST, GEORGE M. *(Univ. of Cincinnati):* Effects of ammonium chloride acidosis on glucose tolerance in dogs. Am. J. Physiol. *168*:126-30, January 1952.

Intravenous glucose tolerance tests with parallel determinations of blood sugar, plasma potassium, and inorganic phosphorus were done on dogs in normal (fasting) states and in states of severe acidosis induced by intravenous perfusions of ammonium chloride solution. Following injections of glucose, the rate of disappearance of sugar from the blood was slower in acidotic than in normal states. The plasma inorganic phosphorus levels in normal states decreased and rose with the rise and fall of blood sugar, but in acidosis they changed less or remained stationary. Changes of plasma potassium did not follow a consistent pattern. States of acidosis

inhibit cellular uptake of sugar, probably by inhibiting processes of phosphorylation.

MANN, GEORGE V.; GODDARD, JAMES W.; AND ADAMS, LUCILE *(Dept. of Nutrition, Harvard Univ. Sch. of Pub. Health, Boston):* The renal lesions associated with experimental diabetes in the rat. Am. J. Path. 5:857-63, September-October 1951.

Weanling male rats were made diabetic with alloxan and studied for periods of 1 to 30 months for the development of cardiovascular lesions. Controlled groups of animals were kept on 1 of 5 types of diet varying in the content of protein and fat. No significant lesions were found in the heart or large vessels. A distinctive lesion was found in the renal glomerular capillaries and consisted of a progressive alteration in reticulin structures. The changes comprised a proliferation of reticulin fibers leading to an obliterative, sclerosing process which progressed eventually to destruction of the entire glomerulus. Unlike lesions of the human disease intercapillary glomerulosclerosis, there was minimal collagenization in the injured glomerulus. Significant arteriolar disease was not apparent, either. In these experiments it was not possible to relate the severity or duration of diabetes to the renal lesions. The nature of the diet could not be shown to have influenced the lesions.

MASKE, HELMUT; WOLFF, HANNS; STAMPFL, BENNO; AND BAUMGARTEN, FRITZ *(Univ. of Munich):* Observations on zinc metabolism in alloxan diabetes. Klin. Wchnschr. 29:671, October 15, 1951.

Following an intravenous injection of 100 mg./kg. of alloxan, significantly increased serum zinc values were recorded. Following the rise in serum zinc values, there was an increased excretion of zinc in the urine. Emission spectrographic determinations did not indicate an increase in the excretion of other metals, except iron. These studies were done on 10 dogs. Histochemically, zinc was not noted in pancreatic sections in significant amounts 4 to 48 hours following injection of alloxan.

MCILWAIN, H.; ANGUIANO, G.; AND CHESHIRE, J. D. *(Biochemical Labs., Inst. of Psychiatry, Maudsley Hosp., London):* Electrical stimulation in vitro of the metabolism of glucose by mammalian cerebral cortex. Biochem. J. 50:12-18, November 1951.

The changing potential gradients which increase the respiration of slices of cerebral cortex also increase their rate of utilization of added glucose and their rate of formation of lactic acid. Respiration and lactic acid formation account to within 6 per cent for the glucose lost during stimulation as well as in its absence. Response to stimulation in vitro is thus in the same direction as in the brain *in situ;* it can be maintained much longer but does not reach rates equal to those which appear to occur during the first few seconds after stimuli are applied in vivo.

MOHNIKE, G. *(Med. Clin. and Polyclin., Univ. of Greifswald, and Res. Inst. for Diabetes, Garz/ Rügen and Karlsburg):* Trials with "Pancreasmellin-Neu:" A contribution to the problem of oral insulin therapy. Die Pharmazie 5:574-77, December 1950.

The purpose of this work was to test "Pancreasmellin-Neu" (PMN) clinically in diabetes. The drug is prepared from fresh pancreatic glands without the addition of chemicals and has excretory as well as incretory action. One tablet is claimed to equal 5 units of injected insulin. The author concludes that this substance does have a certain metabolic effect, which, however, is very slight. The claim that 1 tablet corresponds to 5 units of insulin could not be confirmed. For the treatment of diabetes this preparation, in the doses employed by the author at least, was found unsuited and under certain conditions even dangerous.

MONTAGNA, CARLOS P. *(Buenos Aires):* Treatment of infantile diabetes with NPH insulin. Pamphlet published by the author.

The author reports on 7 patients, between 4 and 10 years of age, all of whom were previously treated with the 2:1 mixture. The control was satisfactory in every case.

MOWRY, ROBERT W.; AND BANGLE, RAYMOND, JR. *(Mallory Inst. of Pathology, Boston City Hosp., Boston):* Histochemically demonstrable glycogen in the human heart, with special reference to glycogen storage disease and diabetes mellitus. Am. J. Path. 4:611-23, July-August 1951.

The periodic acid-leukofuchsin reaction and diastase di-

gestion of duplicate slides as controls are useful procedures in the histochemical study of cardiac glycogen. These methods were applied to the study of glycogen in the myocardium in 33 infants, 63 nondiabetic adults, and 17 diabetic patients. The amounts of histochemically demonstrable glycogen were found to vary widely in hearts of infants, often approaching and sometimes exceeding amounts seen in glycogen storage disease of the heart. In hearts of nondiabetic adults, only slight amounts of glycogen were frequently seen. In a few instances, however, abundant amounts were observed. In hearts of diabetic patients, on the other hand, glycogen was frequently present in moderate and often in large quantities. Increased amounts of histochemically demonstrable glycogen in diabetes mellitus were not clearly related to severity, duration, control, or nature of treatment. The results indicate that extensive glycogen infiltration of the heart is common in infancy and in diabetes mellitus. The presence of massive amounts of histochemically demonstrable glycogen in the myocardium is neither infrequent nor specific for glycogen storage disease of the heart.

NEAL, WILLIAM B., JR.; DRAGSTEDT, LESTER R.; ROGERS, GEORGIANA R.; AND MCKEAGUE, GORDON *(Dept. of Surgery, Univ. of Chicago):* Effect of destruction of thyroid glands by radioactive iodine on pancreatic diabetes in the dog. Am. J. Physiol. *168*:29-32, January 1952.

Radioiodine thyroidectomy in the dog causes an elevation of total serum lipids and cholesterol fractions. The hyperglycemia, glycosuria, hypolipemia, fatty infiltration of the liver, and elevated serum phosphatase of the depancreatized dog are not relieved by I^{131} thyroidectomy, although the insulin requirement is reduced. The depancreatized dog rendered hypothyroid, when fed raw pancreas, shows a greatly exaggerated elevation of total serum lipids and cholesterol.

NIEMEIJER, J. A. *(Lab. of Physiological Chemistry, Univ. of Utrecht, Netherlands):* Construction of a circular Warburg apparatus for 32 manometers. Biochim. et biophys. acta 7:354-65, September 1951.

The construction of the apparatus is described.

OAKLEY, WILFRED *(London, England):* Correspondence. Brit. M. J. 2:1404-05, December 8, 1951.

A plea is made for more conservative surgery in diabetic gangrene of the extremities. Note is made of the importance of the neuritic factor in both young and old diabetics in whom the diabetes is of long duration. Gangrene may occur, in spite of an excellent blood supply, as a result of trauma to an insensitive foot. Reference is made to recent writings on the subject of surgery in diabetic gangrene.

PEISS, C. N.; FIELD, JOHN; AND HALL, VICTOR E. *(Stanford Univ. Sch. of Med., Stanford, Cal.):* Effect of 2,4-dinitrophenol upon anaerobic glycolysis in rat cerebral cortex slices. Am. J. Physiol. *168*:248-50, January 1952.

Over a wide concentration range, 2,4-dinitrophenol has no effect upon the rate of anaerobic glycolysis in rat cerebral cortex slices, as measured manometrically and chemically. Very high concentrations are inhibitory. It has not been possible to demonstrate the augmenting action of dinitrophenol on anaerobic glycolysis in frog muscle. These findings are discussed with relation to the possible correlation of temperature regulation and metabolic activity of the central nervous system.

PETRICK, T. *(St. Paul, Minn.):* Fetal salvage in pregnant diabetic patients. Minnesota Med. 35:28-31, January 1952.

The complication of diabetes mellitus with pregnancy is serious. The solution to all the problems is not at hand. Improvement in fetal salvage in the diabetic patient demands constant observation, thorough care, and regulation. This can be accomplished through vigorous action on the part of the internist, the obstetrician, and the pediatrician.

PITT, C. KERMIT *(Decatur, Ala.):* Galactosemia. J. M. A. Alabama 21:220-26, February 1952.

The author reports a patient with congenital galactosemia who exhibited the characteristic symptomatology of growth failure, hepatomegaly, galactosuria, albuminuria, and cataracts and responded well to management by withdrawal of milk and provision of an adequate diet. Fourteen previously reported cases are briefly summarized.

RODRIGUEZ, RICARDO R.; AND KREHL, WILLARD *(Yale Nutrition Lab., Yale Univ., Dept. of Physiol. Chem., New Haven, Conn.):* The influence of diet and insulin on the incidence of cataracts in diabetic rats. Yale J. Biol. & Med. *24*:103-08, November 1951.

Study was made of the influence of different diets over a period of six months on the incidence of diabetes in rats after subtotal pancreatectomy and on the development of cataracts in partially pancreatectomized and alloxan-diabetic rats.

The incidence of diabetes decreased in 95 per cent of pancreatectomized animals fed a high-protein diet, but only a slight reduction was observed in the incidence and severity of diabetes with the addition of cholesterol or the removal of choline in the high-carbohydrate diet.

Development of cataracts was higher in diabetic rats fed a high-carbohydrate diet; a lesser incidence was observed in high-protein-fed animals; no cataracts developed in rats fed a high-fat diet. The development of diabetic cataracts is directly correlated with the severity of the disease (hyperglycemia and glycosuria) and the duration of diabetes and inversely correlated with the age of the rats.

SAMUELS, SAUL S. *(Atlantic Beach, N.Y.):* Tryptar in the treatment of diabetic gangrene. Angiology 2:589-90, December 1951.

A purified crystalline form of trypsin is now available for local application in cases of diabetic gangrene in which infection is under control. It is claimed that it greatly reduces the healing time of diabetic gangrene. A preliminary method of application of this drug is presented.

SAUGMAN, B. *(Univ. of Copenhagen):* Renal gluconeogenesis in eviscerated cats. Acta physiol. scandinav. *23*:187-95, August 25, 1951.

It has been shown in eviscerated cats that the fall in blood sugar after evisceration is less steep than that observed after evisceration and nephrectomy. In the artificially perfused cat kidney, addition of lactic acid to the perfusion blood was found to evoke a net production of glucose. A pronounced rise in the blood-lactic acid concentration was observed in the eviscerated cat following constriction of the renal stalks.

SCHILIER, J.; PICARD, R.; AND CHIMENES, H. *(Paris):* Use of cortisone in a case of unstable juvenile diabetes. Presse méd. 60:25, January 12, 1952.

Unstable juvenile diabetes occurred in a 12-year-old girl and was successfully treated with cortisone. The total dose of cortisone used (200 mg.) was too low and the course of treatment (14 days) too short for the pancreatic changes to be settled. After treatment, glycemia and glycosuria recovered their previous rates, but hypoglemic accidents definitely disappeared. The authors consider this point to be a further argument in favor of the peripheral tissular action of cortisone, which therefore seems to be the drug indicated for hypoglycemia disorders.

SCHNEEBERG, NORMAN G. *(Res. Dept., Mount Sinai Hosp., Philadelphia):* Serum inorganic phosphorus in the diagnosis of diabetes mellitus. J. Endocrinol. *11*:602-07, June 1951.

An examination was made of the value of determining the serum inorganic phosphorus during the intravenous glucose tolerance test in the diagnosis of diabetes mellitus. Studies in 28 normal controls and in 24 patients with diabetes mellitus demonstrated that phosphate measurements are of aid in diagnosis, although a significant degree of overlap was noted between the two groups. The phosphate response to intravenous insulin was compared with the response to the intravenous injection of glucose. The results suggested that the mild diabetic was capable of secreting insulin and/or utilizing glucose, thus partly explaining the substantial overlap of the phosphate fall in normal subjects and in patients with mild diabetes mellitus.

SCHULITZ, PAUL HUGO *(Hamburg-Barmbek):* Residual carbon in healthy subjects and in diabetics. Ztschr. f. physiol. Chem. 288:149-54, November 1951.

Normal values for residual carbon in blood filtrates and the relationship between residual carbon and nonsugar carbon in diabetics are discussed. Nonsugar carbon values are approximately 60 to 80 mg. per cent in healthy subjects and in some of the diabetic patients. In other diabetics, these values are considerably higher. Possible causes for the difference in the findings of other workers are discussed, e.g., the role of oxyproteinic acids in relation to this question.

SHERRILL, JAMES W. *(La Jolla, Cal.):* Diabetic retinitis; the relationship between retinal degenerative changes and the degree of diabetic control. Bull. Scripps Metabolic Clinic 2:1-17, October 1951.

Among the earliest organic changes found in diabetes is the appearance of capillary microaneurysms in the perimacular area of the retinas. Vision may remain normal for many years in spite of the existence of aneurysms. Retinal changes in diabetes can be retarded for an indeterminate number of years when treatment conforms to the known experimental and clinical laws which regulate diabetes. Ashton has recently shown that microaneurysms are not specific in diabetes and that they are found in approximately 33 per cent of nondiabetic conditions. The lesions do not progress sufficiently in nondiabetic persons to cause visual disturbances except in a very minor percentage. We must consider, therefore, that in diabetes the lesions are activated by the processes which accompany uncontrolled diabetes. Retinitis, then, is not, as Dolger maintains, a counterpart of diabetes.

Rutin is of no value in retinitis; there is evidence to show that it cannot be absorbed from the intestinal tract.

Grave and serious responsibility rests upon the physician who would recommend "free diet," especially since the dangers of uncontrolled diabetes and of hyperglycemia are so well known. The presence of leg cramps, claudication, pruritis, amaurosis, fatigue, polyuria, urticaria, neuritis, etc., in uncontrolled diabetes and the freedom from these symptoms when diabetes is controlled encourage most patients to follow proper caloric restriction. Some of the common causes for failure in the control of diabetes are cited:

1. Consideration of diabetes as a disease of carbohydrate metabolism rather than a disease of total metabolism.
2. Attempts to calculate the diet of the diabetic on the basis of normal caloric requirements. (Diabetes is a condition in which the individual cannot utilize the normal amount of food; hence, the normal dietary does not apply.)
3. Misconception of the number of calories consumed by the average nondiabetic individual. (Many normal women carry on normal work on 1,400 to 1,700 calories daily.)
4. Prescription of insulin for an obviously obese diabetic.
5. Failure to reduce the weight of obese diabetics.
6. Attempts to force-feed or fatten the underweight severe diabetic.
7. Short-cut insulin methods—attempts to control severe diabetes by the use of one daily dose of insulin.
8. The belief that the minimum amount of insulin should be used rather than an adequate amount to control diabetes over the maximum portion of each 24-hour day.

SINGLETON, A. O.; WOLMA, FRED J.; AND POWELL, WILLIAM J. *(Univ. of Texas, Galveston):* Islet cell tumors of the pancreas. M. Rec. & Ann. *46*:833-40, February 1952.

Although over 400 cases of islet-cell adenoma have been reported, the condition is generally not recognized until late in the course of the disease. An attempt should be made to rule out other causes of hypoglycemia before surgery is attempted. Simple excision of the lesions has given good results in most cases, including the suspicious malignant group of adenomas which histologically have the appearance of carcinoma. True islet-cell carcinoma has been an unsolved problem so far, no cures having been reported even after radical surgery.

SOMOGYI, MICHAEL *(Jewish Hosp. of St. Louis):* Mechanism of epinephrine-hyperglycemia. Endocrinology *49*:774-81, December 1951.

Experimental evidence is submitted to show that depression of the rate of peripheral glucose assimilation by epinephrine action plays an important part in the production of epinephrine hyperglycemia.

SOPHIAN, LAWRENCE H.; AND CONNOLLY VALENTINE J. *(U.S.P.H.S., Staten Island, N.Y.):* Chromatographic identification of reducing sugars in urine. Am. J. Clin. Path. *22*:41-45, January 1952.

Paper chromatography can be employed to identify the type of reducing sugar in urine. The Rf values appear to be accurate and characteristic of specific sugars. A special apparatus is described for use with this procedure.

STAMPFL, BENNO; WOLFF, HANNS; MASKE, HELMUT; AND BAUMGARTEN, FRITZ *(Univ. of Munich):* Histochemical examinations in dithizon and alloxan diabetes. Klin. Wchnschr. *29*:671, October 15, 1951.

Okamoto reported a histochemical method by which the zinc content of tissues can be made visible with the aid of diphenylthiocarbazide at a *p*H of approximately 8.6. With this method, pancreatic sections show an especially high zinc content in the islands of Langerhans. They appear purple-red in the barely colored excretory parenchyma. Because of the high zinc content of its islands of Langerhans, the rabbit is especially well suited for histochemical examinations. The red coloration in the island cells appears diffuse at times or in the form of fine to coarse granules. The pancreatic islands of the dog have a much lower zinc content, and the red coloration is not as pronounced. The behavior of zinc in the islands of Langerhans of animals treated with varying doses of dithizon and alloxan was studied histochemically. An almost complete disappearance of island zinc was observed in the dithizon-diabetic animals. Only a trace of pink coloring could be detected. The red granules of the island cells had disappeared. Hematoxylin-eosin staining showed extensive destruction of the islands, such as occurs in alloxan diabetes. What seemed peculiar was the fact that the islands were also free of zinc in alloxan-diabetic animals. The coloration, however, was stronger than in dithizon-diabetic animals. Of further interest is the distribution of zinc in the *a* and β cells. Reports in this respect are forthcoming.

THALER, RICHARD W.; AND WORNAS, CHRISTIAN GEORGE *(Boston):* Coronary arteriosclerosis in diabetics. Am. J. Digest. Dis. *19*:33-37, February 1952.

The fact is re-emphasized that coronary artery disease tends to recur in persons who have had diabetes of long duration. A group of 50 diabetics was studied in an effort to determine the effect of relatively good diabetic control on prevention or postponement of coronary artery disease. Fifteen patients whose diabetic control seemed to have been reasonably good had diabetes an average of 17.7 years before the onset of manifest coronary artery disease and developed coronary artery disease at an average age of 65.6 years. On the other hand, 23 with poor control manifested coronary artery disease after an average of 12 years of diabetes and at an average age of 56.2 years.

Mildness of diabetes seemed to play less of a part in postponement of coronary artery disease than did good control.

VAN BOUWDYK BASTIAANSE, M. A.; AND SINDRAM, I. S. *(Univ. of Amsterdam, Holland):* Diabetes and pregnancy. J. Obst. & Gynaec. Brit. Emp. 58:996-1002, December 1951.

The factors which are probably most deleterious, for both mother and child, are hypoglycemia and acidosis. In 1932, van Bouwdyk Bastiaanse pointed out that pregnant diabetics must be treated with a diet rich in carbohydrates, with enough insulin to maintain a normal blood sugar level. The amount of fat must be restricted for the same reason and because many diabetics are overweight. The amount of insulin necessary should not be estimated according to the quantity of sugar excreted in the urine but according to the blood sugar level. A change in the renal threshold in both directions can further complicate the situation. All these problems cannot be managed by the obstetrician alone, and every pregnant diabetic must be under the careful supervision of an internist as well. Other possible therapeutic measures are the administration of large quantities of hormones or synthetic estrogen and the termination of pregnancy about the 37th week, preferably by means of cesarean section. The literature at the present moment is far from unanimous on both these subjects. Although the authors are convinced that a cesarean section is more frequently indicated in the diabetic woman because of a large child, postmaturity, toxemia, they do not see any reason for a routine cesarean in the 37th week.

VAN DER KLEIJ, B. J. *(Lab. of Physiological Chemistry, Univ. of Utrecht, Netherlands):* A rapid determination of glycogen in tissues. Biochim et biophys. acta 7:481-82, September 1951.

A quick method for the determination of glycogen in tissues has been elaborated by combining a rapid procedure of extraction, viz., grinding the tissue sample with sand and trichloroacetic acid, with the very simple spectrophotometric method of glucose determination according to Mendel and Hoogland. The latter makes use of a pink color which develops when concentrated sulphuric acid is added to a glucose solution and the mixture is placed in a boiling water bath for a few minutes. The glycogen need not be hydrolyzed before the glucose determination is performed because 7 minutes' heating with the only slightly diluted sulphuric acid is sufficient to bring about hydrolysis of the glycogen as well as development of the color. The efficiency of ex-

traction and hydrolysis were checked by Pflüger's method: liberation and isolation of glycogen by treatment of the tissue with 60 per cent KOH, precipitation and washing of the glycogen with ethanol, followed by hydrolysis with normal sulphuric acid in a boiling water bath for 2 hours. From the good agreement observed between the results obtained with both methods, the lengthy procedure of Pflüger may be replaced by this rapid determination, which offers great advantages for routine analyses.

WATTS, D. T. *(Charlottesville, Va.):* The effect of morphine and pentobarbital on ether hyperglycemia. Anesthesiology *13*:33-37, January 1952.

The effect of morphine and pentobarbital on ether hyperglycemia in rabbits has been investigated. Morphine has no effect on ether hyperglycemia, whereas pentobarbital inhibits this rise in blood glucose. The possible relationship of these observations to surgical anesthesia is discussed.

WILMOT, VALERIE A.; AND SWANK, ROY L. *(Montreal Neurological Inst., Montreal):* The influence of low-fat diet on blood lipid levels in health and in multiple sclerosis. Am. J. M. Sc. *223*:25-34, January 1952.

Fasting blood lipid levels were determined weekly for control periods up to 8 weeks in normal subjects and in patients with multiple sclerosis and during study periods up to 12 weeks on low-fat diets containing 30 to 50 grams of fat daily.

No essential differences were found between normal subjects and patients with multiple sclerosis with respect to either lipid levels or the response of lipid levels to the change in diet.

Lowering of the fat intake produced a temporary reduction of total lipids, with the phospholipid and cholesterol levels both decreasing together to reach their lowest values at an average of 5 weeks after institution of the diet. Studies 5 to 13 months later indicated that the reduction in cholesterol was maintained, but the phospholipid tended to return to its predietary level.

WOLFF, HANNS; MASKE, HELMUT; STAMPFL, BENNO; AND BAUMGARTEN, FRITZ *(Univ. of Munich):* Dithizon diabetes. Klin. Wchnschr. *29*:670-71, October 15, 1951.

Dithizon (diphenylthiocarbazone) was used to produce diabetes in rabbits. Transient to permanent forms resulted, depending upon the dose. Histological examination of the pancreatic tissue from these animals disclosed severe damage to the islands of Langerhans. Histochemical tests revealed a significant decrease in the zinc content of the islands. Urine examinations showed an increased zinc excretion following medication. Except for a slight increase in iron excretion, there was no rise in the excretion of other metals.

ZIMMERMAN, HYMAN J.; PARRISH, ALVIN E.; AND ALPERT, LOUIS K. *(V. A. Hosp. and George Washington Univ. Sch. of Med., Washington, D.C.):* Failure of testosterone to alter the responsiveness to insulin in diabetes mellitus. Proc. Soc. Exper. Biol. & Med. *77*:646-48, August 1951.

The administration of testosterone propionate in doses of 10, 25, or 50 mg. daily for a period of ten days to thirteen patients with diabetes mellitus failed to alter significantly the responsiveness to insulin in all but one. The authors suggest that the presence of the side chain attached to carbon atom 17 in the steroid molecule may be essential for this activity.

ZUBROD, CHARLES G.; EVERSOLE, STANTON L.; AND DANA, GEORGE W. *(Johns Hopkins Hosp., Baltimore):* Amelioration of diabetes and striking rarity of acidosis in patients with Kimmelstiel-Wilson lesions. New England J. Med. *245*:518-25, October 4, 1951.

A study was made of the effect of renal disease on the severity of diabetes in 190 cases eventually autopsied at the Johns Hopkins Hospital. The cases were divided into three groups on the basis of their renal lesions: those with Kimmelstiel-Wilson lesions, those with other types of renal lesions, and those with no renal lesions. The basal insulin requirement of the Kimmelstiel-Wilson group was fully as high as that of the two control groups. The diabetics with Kimmelstiel-Wilson lesions required progressively less insulin during the course of the disease; the diabetics without these lesions required progressively more. There was virtual absence of acidosis throughout the entire duration of diabetes in patients with Kimmelstiel-Wilson lesions.

EDITORIALS

THE ANNUAL MEETING

The founders of the American Diabetes Association originally established the Annual Meeting in the belief that it would be a major interest of the Membership. Since then the Association has developed new and varied functions, but the Annual Meeting continues to hold its place of importance.

The details of the Program for the Meeting in June 1952 are presented elsewhere in this issue of the Journal. It includes a well-balanced selection of scientific papers dealing with both investigation and practice. The highlight will be the Banting Memorial Lecture, to be delivered by Professor Charles H. Best.

A joint session with the Endocrine Society will again be held. Since the two Societies have numerous interests which coincide and since many of our members belong to both, the combined sessions held in recent years have proved mutually advantageous.

The panel discussions which were tried with success last year will be repeated at this meeting. Members are urged to submit questions which they wish answered for their own information and for the general interest of the audience.

The banquet will provide an occasion for sociability. It also promises to be a noteworthy event in the history of the Association for reasons which will be revealed in due time.

The Scientific Sessions will be followed by a Conference of Affiliate Associations, which will permit exchange of ideas and development of projects to serve diabetics throughout the continent. Mention should also be made of the activities carried on in advance of the Scientific Sessions. The year-round activities of the Association are largely determined by work done during meetings of the Council and the Committees held at this time.

The Twelfth Annual Meeting at Chicago promises to be unusually valuable and productive for the Association and its Members.

BIOLOGICAL ANTAGONISM

The concept of the "essential metabolite" as the keystone of metabolic processes has been generally accepted in modern biological thought. In tracing pathways of the intermediary metabolism of such metabolites, the use of isotopes has been extremely valuable. A second approach to such investigations is the use of an analogue of a metabolite which competes with the metabolite for a biological substrate but is unable to substitute for it in the subsequent metabolic reactions. The result is an interference with an essential metabolic process.

Such an interference may have widespread uses and effects. For example, it may lead to the discovery of a new metabolite, as in the case of para-amino benzoic acid, or to the discovery of a new function of a previously known metabolite, such as the demonstration that tryptophane may be a precursor of nicotinic acid. By the proper choice of such antagonistic agents, it may be possible to explore the steps in various metabolic

syntheses and transformations. An early application of this procedure led to the recognition of a possible chain reaction in purine synthesis. In many instances, the antagonism between structurally related agents may serve to maintain physiological order as evidenced by the beneficial antagonism between potassium and sodium ions, or between testosterone and various estrogens. In still other instances, the process of blocking cellular reactions may disturb physiological order with a net result which is beneficial to the organism. The antagonism between dicoumarol and vitamin K with its anticoagulant effect and that between acetyl-choline and prostigmine which results in an anticholinesterase effect are typical examples. At times, the blocking effect may inhibit growth or cause death of the cell. Hence, the phenomenon may be applied to the fields of bacteriology, virology, and cancer research.

The concept of biological competition, or antagonism, has achieved sufficient importance to merit three recent and important reviews[1, 2, 3] which should be of considerable interest to the medical profession. In these reviews, the application of the concept to pharmacology, chemotherapy, physiology, and biochemistry covers such diversified units as antibacterial agents, vitamins, amino acids, purines, pyrimidines, steroid hormones, antithyroid compounds, a variety of drugs, simple ions, and antiviral substances. Both synthetic and naturally-occurring antagonists have been investigated. The former have been applied largely to the field of therapeutics and include such substances as sympathetic-blocking agents, antihistamines, sulfonamides, and folic acid antagonists. The latter may be extremely important in the maintenance of biological order through the stabilization which results from antagonisms between ions, or amino acids, or hormones.

Although the concept is not a new one, the discovery of the competition between sulfonamides and para-amino benzoic acid has resulted in the renaissance of a somewhat neglected idea. It seems to hold a clue not only to the etiology of certain diseases and the therapy of others, but also to the maintenance of order in the constant flux of physiological processes.

—ROSEMARY MURPHY, M.D.

REFERENCES

[1] D. W. Woolley, Consulting Editor: Antimetabolites, Ann. N.Y. Acad. Sci. 52:1197-378, 1950.

[2] Martin, G. J.: Biological Antagonism. The Theory of Biological Relativity. New York, The Blakiston Company, 1951.

[3] Woolley, D. W.: A Study of Anti-metabolites. New York, John Wiley & Sons, Inc., 1952.

PATIENT EDUCATION AND THE A.D.A. FORECAST

The *A.D.A. Forecast* is the Association's foremost means of direct service to the diabetic patient. A great deal of time, thought, and effort have gone into the continued development and improvement of this publication, under both its original editorial guidance and its current management by Frederick W. Williams, M.D., Editor in Chief, and Mr. Groff Conklin, Managing Editor. Since it began publication in 1948, the magazine has proved its usefulness for many types of diabetics.

The value of the *Forecast* to the individual diabetic is easy to describe. It gives him practical information to help him in his day-by-day diabetic regimen. It prepares him for problems which may confront him in the future. It strengthens him by giving a feeling of solidarity and fellowship with the many others like himself—other diabetics with the same problems, frustrations, discomforts and complications. One of the magazine's popular and effective departments is "The Funny Side," in which diabetics enjoy a laugh at themselves or at the non-diabetic outside world. Finally, the *Forecast* helps the patient to free himself from needless anxiety and unhappiness. Letters are frequently received from readers who express their satisfaction at finding that others have learned how to cope with diabetic problems, and who say that because of the magazine they no longer feel so isolated or so different.

An effort is constantly being made by the Editors of the *Forecast* to broaden its scope and make it of interest to a wider segment of the diabetic population. This is not a simple task, since diabetics are of all ages, educational levels, tastes, and degrees of sophistication. As consistently as possible, the magazine has been kept firmly in the middle of the road, so that diabetics of nearly every type, barring the semiliterate, will be able to find something in it to their taste.

The *Forecast* is useful to physicians as well. They find the magazine an aid in their efforts to teach their patients and to secure their cooperation in achieving good diabetic management.

Finally, the *Forecast* helps the Association to bring itself to the attention of diabetics everywhere. It is the most effective means, outside of individual correspondence, of providing—as an Association—direct assistance to persons with diabetes. It does not trespass on the intimacies of the doctor-patient relationship, being careful not to intrude medical advice when that advice should be given personally. Yet it makes constant and fairly successful efforts to set diabetics straight on many knotty problems and obscure questions; two examples

from the current issue concern the facts about the alleged claim that a tea for diabetics would eliminate the need for insulin, and information regarding the nature and cause of hemochromatosis.

With the advice of the medical Editorial Advisory Board, and the good judgment of its Editor in Chief, the *Forecast* cannot fail to be useful to diabetics from the point of view of providing sound and useful information about their condition. This statement will hold true, however, only as long as articles presenting needed information are forthcoming from the medical profession. The future of the *Forecast* depends both on the willingness of members of the Association to contribute original medical papers, and on the enthusiasm and persistence with which physicians recommend the magazine to their diabetic patients. The Editors report that there is rarely a scarcity of lay contributions. Diabetics seem to enjoy writing about their experiences and expressing their opinions; the only problem the Editors face in this connection is the unpleasant one of having to reject unacceptable contributions.

However, nontechnical but informative articles on the nutritional, metabolic, physiological and psychological problems of diabetes are less easily secured, according to the Editors. If any members of the Association would like to help, they should first examine recent issues of the magazine to find out what has already been published; then they should write the Editors and offer to prepare a simple article on some medical subject of general interest to diabetics. If the subject has not already been covered, their papers will be welcome. Prospective contributors can be assured that each article submitted will be studied thoroughly, and that the selection for publication will be fair and unbiased.

BOOK REVIEWS

THE FACTS OF LIFE FROM BIRTH TO DEATH. *By Louis I. Dublin, Ph.D., in collaboration with Mortimer Spiegelman. Cloth. $4.95. Pp. 461 plus index. The Macmillan Co., New York, 1952.*

A volume by the distinguished Second Vice President and Statistician of the Metropolitan Life Insurance Company concerning the vital statistics of life and death merits serious critical consideration. Here is a work of over 460 pages, containing a large amount of information of significance to the doctor, lawyer, statistician, and most of all to the intelligent citizen. In 25 chapters Dr. Dublin and his collaborator cover the major highlights of modern living in relation to health. From an illuminating picture on who we are and the nature of our population, through various subjects such as the needs and problems of the average American family, the care of the sick, changes in mortality, and the specific problems created by the various major diseases and causes of death, they follow in proper sequence.

An unusual and worthwhile chapter deals with the control of diabetes. Here in a relatively few pages one finds the answers to a great many of the questions that come to mind concerning diabetes and its control. Following this there appears a broadening comment on the circulatory diseases and on rheumatic disorders.

Topics such as the problems of our older people, the toll of accidents, the hazards of various occupations, all are dealt with in a most readable style, as are the present status of mental health in America, the situation concerning public health and public health administration, and, finally, the prospects and problems of longevity.

The question and answer form in which the book is cast makes for readability, and interest is sustained throughout by the compact consideration of each topic and the natural sequence with which the reader passes from one aspect of the subject to another. He will, indeed, have considerable difficulty in laying this volume aside once he begins to turn its pages.

Not the least of its values is the fact that this work

can be used as a ready reference for all kinds of information about "the facts of life." There is no doubt that the distinguished author has equalled, and probably surpassed, his previous efforts in this general area of consideration. The book is heartily recommended to the medical profession, and to all clinical and allied groups.

THE PATHOLOGY OF DIABETES MELLITUS. *By Shields Warren, M.D., Depts. of Pathology, New England Deaconess Hospital and Harvard Medical School, Boston, and Director, Division of Biology and Medicine, U. S. Atomic Energy Commission; and Philip M. LeCompte, M.D., Depts. of Pathology, Faulkner Hospital and Harvard Medical School. Third edition. Cloth. $7.50. Pp. 336. Illustrated. Lea & Febiger, Philadelphia, 1952.*

In the third edition of this well-known monograph, Warren, now assisted by LeCompte, presents both old and new information regarding diabetes and associated conditions. The book is based on observations made on more than 800 cases of diabetes mellitus studied at necropsy, supplemented by an extensive review of the literature.

It presents first a detailed study of the histology of the pancreas in normal and diabetic persons. Then follows a review of anatomical evidences of abnormal carbohydrate and fat metabolism; next, a report of the changes seen, in the presence of diabetes, in various organs including the blood vessels, heart, kidneys, eyes, and nervous system. Of particular interest are the chapters dealing with the pathology of diabetes in children and the infants of diabetic mothers.

The authors do not limit their discussion to the structural changes seen by the eye of the pathologist; this is well illustrated by the section on the etiology and pathogenesis of diabetes. The fact that in a third of the cases autopsied there appeared no anatomical change in the pancreas or other organs has puzzled the pathologist. The authors point out that newer histological methods are likely to show that many of these cases with apparently normal islets in the pancreas actually have a marked reduction in the number of beta cells or an increase of alpha cells, or both; also that the total volume of the "islet organ" may be altered.

As an example of the conclusiveness with which a postmortem diagnosis of diabetes can be made under favorable circumstances, the authors cite the case of a woman 50 years of age who died from coronary occlusion. She had no history of diabetes, but at the autopsy sugar and acetone were found in the urine taken from the bladder. "Microscopic examination revealed the following: abundant glycogen in the renal tubules, occasional small granules of glycogen in the beta cells in the islands of Langerhans, a beta to alpha cell ratio of approximately 2.7 by the Gros-Schultze method, and typical intercapillary glomerulosclerosis in the kidneys. There were thus no less than five significant findings, any one of which might be considered as adequate presumptive evidence of diabetes, while all five taken together establish the diagnosis beyond doubt, regardless of the negative clinical history. Incidentally, of course, a coronary occlusion in a woman of 50 is in itself sufficient to raise a very strong suspicion of diabetes."

Students of diabetes will find in this volume a mine of interesting and valuable information.

BODY, MIND, AND SUGAR. *By E. M. Abrahamson, M.D., and A. W. Pezet. Cloth. $3.95. Pp. 206 with 12 illustrations. Henry Holt & Co., Inc., New York, 1951.*

One finds listed on the cover jacket chronic fatigue, allergies, asthma, peptic ulcers, rheumatoid arthritis, neuroses, alcoholism, drug addiction, insanity, suicide, murder, followed by the statement: "For the estimated ten to thirty million Americans affected by these conditions, 'Body, Mind, and Sugar' brings new hope for health and happiness. The book is about sugar starvation (hyperinsulinism)—a vital but little known medical discovery which was first revealed some year ago, but which only today is coming to be understood generally by the medical profession."

There is, indeed, need for physicians to be alert to discover hypoglycemia in relation to symptoms which appear at the time of hunger and disappear after eating. Yet the medical profession must avoid placing exaggerated emphasis on minor changes in the blood sugar level and in the sugar tolerance blood sugar curves. There would appear to be very inadequate justification for the claim that many million Americans are affected by abnormal lowering of blood sugar. The lay reader will certainly be led astray by such statements.

Bernhard Naunyn

Rollin T. Woodyatt, M.D.
CHICAGO

Naunyn was born in 1839, and died in 1925 at the age of 86. His father was a Berlin burgomaster who came from East Prussia, as did Naunyn's mother and his wife. All three families could trace their ancestry back in that region for several hundred years. Koenigsberg was Naunyn's actual home. His autobiography, "Erinnerungen, Gedanken und Meinungen,"[1] tells of annual vacations in the East Prussian woods and the scenery of that country.

As a student at Bonn, he concentrated heavily on zoology and anatomy under Lieberkühn and Wagener. Then, impressed by von Frerichs, he devoted himself wholly to internal medicine, first as an amanuensis, later as second and first assistant in the Frerichs clinic. Among his associates here were Mannkopf, Ries, Quincke, Nencki and Schulzen. They were disciples of Johannes Müller, father of general physiology, and were applying his principles of experimental science in their studies of clinical problems. And as this was a period in which the works of Liebig and his pupils were exciting great interest in organic chemistry as applied to physiology and pathology, they leaned to the study of problems in pathological chemistry and metabolism. Naunyn fell in with the spirit of the group and eventually became its leading exponent, to such an extent that after his death Frederich Müller rated him as "the last of those truly great men who lifted German medicine to the level of a natural experimental science." He was Professor of Medicine at Dorpat in 1868, at Berne and then at Koenigsberg in 1872, and finally at Strassburg where he succeeded Kussmal in 1888. In 1872, with Schmiedeberg and Klebs, he founded the "Archiv für experimentelle Pathologie und Pharmacologie" and remained one of its editors to the end of his career. Schmiedeberg and Naunyn were both professors at Dorpat between 1870 and 1872, both leaving the same year. While Naunyn was in Koenigsberg, Schmiedeberg was in Strassburg, where the two were reunited in 1888. In the meantime (1877) there appeared in the "Archiv" the experimental study on the "Action of Acid in the Animal Body," by Frederich Walter, a Schmiedeberg pupil, which laid the foundations of the conception of "acidosis" (so named and first defined by Naunyn).

The works of Naunyn from 1862 to 1909 are collected in two volumes, published by his wife.[2] These and his later works were critically reviewed in a biographical sketch by Fredrich Müller in 1926.[3] They deal with many topics other than diabetes. An early work on echinococcus demonstrated the development of taenia echinococcus hominis in dogs after feed-

ings of cysts and, by chemical examination, inosit, leucin, and succinic acid but no albumin in the fluid content of cysts and therewith a distinction from exudates, transudates and purulent fluids which led to further studies of the chemistry and pathogenesis of such fluids in general. This was followed by a series of studies of icterus and related problems, the chemistry of bile pigments, hemolytic icterus, the chemistry and pathogenesis of biliary calculi. The studies drew attention to the role of bacteria in calculus formation, originated the conception of "cholangiitis" as the underlying condition and established the principle of treatment by surgical drainage. In this case, as in others, the selection of a theme with medical and surgical angles was in keeping with a firm belief in interdepartmental cooperation, which also found expression in his founding of the periodical *Grenzgebiet der Medicine und Chirurgie.* Added to such works were numerous and significant writings on neurological problems and a variety of other clinical topics.

His interest in diabetes began in the Frerichs clinic when the science of metabolism was still in the cradle. He was a pioneer in the use of the quantitative diet in the study and management of diabetes. In an early work he showed the production of sugar from protein and the necessity of limiting protein as well as carbohydrate in the diets of diabetics. This necessity had been mentioned indefinitely by Rollo, Prout and Bouchardat, but Cantani was the first to state it in definite terms, and he and Naunyn were responsible for its recognition. Even more than Cantani, Naunyn stressed the importance of really quantitative measurements of all elements of the diet and of limiting the total caloric magnitude. To bring about the aglycosuric state and its attendant effects on tolerance, or to reduce glycosuria to minimum levels in the most severe cases, he pushed the principle to the point of undernutrition. The interpolation of days on which the diet was noncaloric except for a possible allowance of alcohol ("Hungertage") was a practice that appears to have started in Naunyn's clinic. The application of the principle was extended by his pupils, especially Weintraud. It was also notably expanded by F. M. Allen.

We have spoken of the study of Walter which painted the picture of coma in acid-poisoned rabbits. Its similarity to the clinical picture of diabetic coma could scarcely have escaped Naunyn's attention. It was rendered more striking by Hallervorden, who in a study of the ammonia in the urine in pathologic conditions observed its increase in severe diabetes (confirming an observation of Boussingault made in 1852). Then Stadelmann, distilling the urine of patients in diabetic coma, recovered large quantities of a volatile acid. This was *a* crotonic acid, but it was shown by Minkowski to have been derived from β hydroxybutyric acid in the process of distillation. The quantities were then measured by a method developed by Magnus Levy, and compared with the amounts used to produce coma in Walter's experiments. The two were in agreement. Then finally Minkowski analyzed the blood of a comatose patient for carbon dioxide as Walter had done in rabbits and again the figures agreed with those obtained by Walter, completing the identification. All of the above-mentioned writers, with the exception of Walter, were pupils of Naunyn. Their work made it apparent that an overproduction of acid from endogenous sources, proceeding at a sufficient rate, may result in a diminution of the alkaline reserve and eventually coma when the diminution is sufficient. The term "acidosis" was coined by Naunyn to mean a metabolic anomaly characterized by an overproduction of acid (any kind of acid) from endogenous sources. To the fall of the alkaline reserve, when this occurs, he applied such terms as "hypoalkalinity," "alkalipenia," or "alkali deficit."

Naunyn's master work was the second edition of his treatise on diabetes, "Der Diabetes Melitus," 1906.[4] This book contains the gist of his personal researches and those of his pupils, together with later reflections. Although out of date now in some respects, it is still a granary of ideas and factual data of very great importance to the modern student.

REFERENCES

[1] Naunyn, B.: Erinnerungen, Gedanken und Meinungen (Memories, Reflections and Impressions). Munich, J. F. Bergmann, 1925, 571 pp.

[2] Naunyn, B.: Gesammelte Abhandlungen von Bernhard Naunyn. Würzburg, University Press, H. Stutz, 1909, 2 vols.

[3] Müller, Fr.: Bernhard Naunyn. Deutsch. Arch. klin. Med. 150:1, 1926.

[4] Naunyn, B.: Der Diabetes Melitus. Vienna, Alfred Holder, 1906.

ORGANIZATION SECTION

Program

TWELFTH ANNUAL MEETING

AMERICAN DIABETES ASSOCIATION

THE DRAKE, CHICAGO, ILL.

JUNE 7 AND 8, 1952

REGISTRATION

June 6 — Upper Lobby
June 7 & 8 — French Room Foyer
9:00 a.m. to 6:00 p.m.

SCIENTIFIC SESSION

JOINT MEETING WITH THE ENDOCRINE SOCIETY
Saturday, June 7, at 2:00 p.m.
PALMER HOUSE — Red Lacquer Room
Gregory Pincus and Arthur R. Colwell presiding

Spontaneous Disappearance of Alloxan Diabetes in the Rat after 12-20 Months of the Disease

ARNOLD LAZAROW, Western Reserve University School of Medicine, Cleveland, Ohio.

Discussion opened by ALEXANDER MARBLE, New England Deaconess Hospital, Boston, Mass.

Multiple Endocrine Adenomas: Report of 8 Cases Involving the Parathyroids, Pituitary and Pancreas

LAURENTIUS O. UNDERDAHL, LEWIS B. WOOLNER (by invitation) and B. MARDEN BLACK (by invitation), Mayo Clinic, Rochester, Minn.

Some Further Studies on the Relationship of Adrenal Cortex Hormones to Experimental Diabetes

DWIGHT J. INGLE, Research Division, Department of Pharmacology, The Upjohn Company, Kalamazoo, Mich.

Discussion opened by GEORGE W. THORN, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

The Evidence for Acceleration of Neoglucogenesis from Fat by ACTH, Cortisone, and Related Compounds

LAURANCE W. KINSELL, GEORGE D. MICHAELS (by invitation), SHELDEN MARGEN, LENORE BOLING (by invitation) and JOHN W. PARTRIDGE (by invitation), Institute for Metabolic Research of the Highland-Alameda County Hospital, Oakland, Calif.

INTERMISSION (10 MINUTES)

Insulin — Banting Memorial Lecture

CHARLES H. BEST, Director, Banting and Best Department of Medical Research and the Department of Physiology, University of Toronto, Toronto, Ont.

Studies on Steroid Diabetes in Man

JOHN J. BOOKMAN (by invitation), STANLEY H. DRACHMAN (by invitation), LOUIS E. SCHAEFER (by invitation) and DAVID ADLERSBERG, The Mount Sinai Hospital, New York, N.Y.

Discussion opened by PETER H. FORSHAM, University of California Medical School, San Francisco, Calif.

ANNUAL BANQUET

Saturday, June 7, at 7:00 p.m.
THE DRAKE—Gold Coast Room
Address of the President: ARTHUR R. COLWELL

Presentation: "Past, Present and Future of the American Diabetes Association"—HERMAN O. MOSENTHAL, JOSEPH T. BEARDWOOD, JR., CECIL STRIKER

Presentation of the Banting Memorial Medal to ROBERT RUSSELL BENSLEY, Professor Emeritus of Anatomy, University of Chicago, The School of Medicine, Chicago, Ill.

Presentation of Award to Banting Memorial Lecturer, CHARLES H. BEST, by ELLIOTT P. JOSLIN

SCIENTIFIC SESSION

Sunday, June 8, at 9:00 a.m.
THE DRAKE—Grand Ballroom
Arthur R. Colwell presiding

The Role of Potassium in the Reduction of Mortality from Diabetic Coma

JOSEPH H. CRAMPTON, The Mason Clinic, Seattle, Wash.

Discussion opened by CLIFFORD F. GASTINEAU, Mayo Clinic, Rochester, Minn.

Effects of Acidosis on Insulin Action and on Carbohydrate and Mineral Metabolism

GEORGE M. GUEST, BRUCE MACKLER (by invitation) and HARVEY C. KNOWLES, JR., University of Cincinnati College of Medicine, Cincinnati, Ohio.

Discussion opened by T. S. DANOWSKI, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

The Significance of the Harmoniously Timed Insulin Dosage in the Treatment of Severe Diabetes

JAKOB S. MOLLERSTROM, Department of Metabolic Research, Wenner-Grens Institut, Stockholms Hogskola, Stockholm, Sweden.

Discussion opened by CHARLES H. BEST, University of Toronto Faculty of Medicine, Toronto, Ont.

The Insulin Content of Blood Plasma

J. BORNSTEIN (by invitation), Washington University School of Medicine, St. Louis, Mo.

Discussion opened by EVELYN ANDERSON (by invitation), National Institutes of Health, Bethesda, Md.

Roentgen Therapy in Diabetic Retinopathy

ROBERT H. TRUEMAN (by invitation), JOSEPH T. BEARDWOOD, JR. and JULIUS J. SMITH (by invitation), University of Pennsylvania School of Medicine, Philadelphia, Pa.

Discussion opened by HOWARD F. ROOT, New England Deaconess Hospital, Boston, Mass.

INTERMISSION (5 MINUTES)

A Survey of Tuberculosis Among Diabetics

EDWARD S. DILLON, RUSSELL RICHARDSON, KATHARINE R. BOUCOT (by invitation), DAVID A. COOPER and PAUL MEIER (by invitation), University of Pennsylvania School of Medicine, Philadelphia, Pa.

Discussion opened by JOSEPH B. STOCKLEN (by invitation), Western Reserve University School of Medicine, Cleveland, Ohio.

The Metabolism of Fructose in Diabetic Subjects

MAX MILLER, J. W. CRAIG (by invitation), H. WOODWARD, JR. (by invitation), J. E. OWENS (by invitation), W. DRUCKER (by invitation) and J. MURPHY (by invitation), Western Reserve University School of Medicine, Cleveland, Ohio.

Discussion opened by RACHMIEL LEVINE (by invitation), Michael Reese Hospital, Chicago, Ill.

The Electroencephalogram of Patients with Diabetes Mellitus

JOSEPH L. IZZO, DANIEL B. SCHUSTER (by invitation) and GEORGE L. ENGEL (by invitation), University of Rochester School of Medicine, Rochester, N.Y.

Discussion opened by MAXIMILIAN FABRYKANT, New York University Post-Graduate Medical School and The University Hospital, New York, N.Y.

PANEL DISCUSSIONS*

Sunday, June 8, at 12:00 noon
THE DRAKE

Factors in the Pathogenesis of Diabetes (Walton Room)

FRANCIS D. W. LUKENS, Moderator, University of Pennsylvania School of Medicine, Philadelphia, Pa.

CHARLES H. BEST, University of Toronto Faculty of Medicine, Toronto, Ont.

JEROME W. CONN, University of Michigan Medical School, Ann Arbor, Mich.

SAMUEL SOSKIN, Michael Reese Hospital, Chicago, Ill.

GEORGE W. THORN, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

Complications and Sequelae of Diabetes: Relation to Control (Gold Coast Room)

HENRY T. RICKETTS, Moderator, University of Chicago, The School of Medicine, Chicago, Ill.

ROBERT L. JACKSON, State University of Iowa College of Medicine, Iowa City, Ia.
Growth and Development

E. T. BELL, University of Minnesota Medical School, Minneapolis, Minn.
Systemic Arteries

EDWARD TOLSTOI, New York Hospital, New York, N.Y.
Nephropathy

HOWARD F. ROOT, New England Deaconess Hospital, Boston, Mass.
Cataract and Retinopathy

ROBERT W. SCHNEIDER, Cleveland Clinic, Cleveland, Ohio.
Neuropathy

Diabetic Acidosis and Coma: Prevention and Management (French Room)

ALEXANDER MARBLE, Moderator, New England Deaconess Hospital, Boston, Mass.

JOSEPH H. CRAMPTON, The Mason Clinic, Seattle, Wash.

EDWARD S. DILLON, University of Pennsylvania School of Medicine, Philadelphia, Pa.

GEORGE M. GUEST, University of Cincinnati College of Medicine, Cincinnati, Ohio.

WILLIAM R. JORDAN, University of Virginia Department of Medicine, Richmond, Va.

HERBERT POLLACK, The Mount Sinai Hospital, New York, N.Y.

*It is requested that questions for the panels be sent to the National Office in advance, or left at the Registration Desk prior to 10:00 a.m., Sunday, June 8.

ANNUAL BUSINESS MEETING

Sunday, June 8, at 2:00 p.m.
THE DRAKE—Grand Ballroom

Reports of officers, election of officers and councilors, and induction of president-elect.

SCIENTIFIC SESSION

Sunday, June 8, at 2:30 p.m.
THE DRAKE—Grand Ballroom
Frank N. Allan presiding

Changes in Blood Glucose in Response to Stress and Their Relevance to Diabetes Mellitus

LAWRENCE E. HINKLE, JR. (by invitation) and STEWART WOLF (by invitation), New York Hospital, New York, N.Y.

Discussion opened by ARTHUR R. COLWELL, Northwestern University Medical School, Chicago, Ill.

Hormones and the Metabolism of Isolated Tissues

M. E. KRAHL (by invitation), Washington University School of Medicine, St. Louis, Mo.

Discussion opened by FRANCIS D. W. LUKENS, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Infantile Diabetes

HARRY W. FARRELL (by invitation), ALBERT M. HAND (by invitation) and ALVAH L. NEWCOMB, Children's Memorial Hospital, Chicago, Ill.

Discussion opened by ROBERT L. JACKSON, State University of Iowa College of Medicine, Iowa City, Ia.

SYMPOSIUM ON LIPOPROTEINS IN DIABETES MELLITUS

Ultracentrifugal Studies of Diabetic Serum

MARTIN HANIG (by invitation) and MAX A. LAUFFER (by invitation), University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Serum Lipids and Lipoproteins in the Kimmelstiel-Wilson Syndrome

HYMAN ENGELBERG (by invitation), HARDIN D. JONES (by invitation) and JOHN W. GOFMAN (by invitation), University of California, Berkeley, Calif.

Atherosclerosis, Arteriosclerosis and S.F. Fat Particles: Preliminary Report on 1,000 Cases of Diabetes Mellitus

JOSEPH H. BARACH and ALEXANDER D. LOWY, JR., University of Pittsburgh School of Medicine, Pittsburgh, Pa.

The Serum Cholesterol and Lipoprotein Levels in Young Patients of Long Duration

NILS KEIDING (by invitation), GEORGE V. MANN (by invitation), HOWARD F. ROOT and ALEXANDER MARBLE, New England Deaconess Hospital, Boston, Mass.

Discussion opened by JOHN W. GOFMAN (by invitation), University of California Berkeley, Calif., and ALEXANDER MARBLE, New England Deaconess Hospital, Boston, Mass.

BY TITLE

Postprandial Glycosuria in Mild Diabetes Mellitus

PALMER H. FUTCHER and GASTON SAUVE (by invitation), Johns Hopkins Hospital, Baltimore, Md.

Group Psychotherapy in the Treatment of the Obese Diabetic

JOSEPH I. GOODMAN and EDWARD SCHWARTZ, Cleveland Heights, Ohio.

The Use of Oxygen in Hypoglycemia Associated with Anoxia

BARNETT GREENHOUSE, New Haven, Conn.

Psychological Factors Affecting Treatment of the Diabetic Child

WILLIAM A. HAWKE (by invitation), MARY EDDIS (by invitation) and RENEE DAVID (by invitation), Hospital for Sick Children, Toronto, Ont.

Observations and Experiences at a Summer Camp for Diabetic Children

HARRY G. JACOBI, New York University College of Medicine, New York, N.Y.

Overinsulinization of Diabetic Patients

HENRY J. JOHN, Cleveland, Ohio.

Clinical Usefulness of the Wilkerson-Heftmann Blood Sugar Test

MORRIS MARGOLIN and HAROLD E. GENTRY (by invitation), University of Nebraska College of Medicine, Omaha, Nebr.

Neurogenic Bladder as a Complication of Diabetes, Diagnosis and Treatment: Report of 7 Cases

MAXWELL SPRING and JESSE HYMES (by invitation), Bronx, N.Y.

CONFERENCE OF AFFILIATE ASSOCIATIONS

Monday, June 9, at 12:30 p.m.
THE DRAKE—Gold Coast Room
Luncheon Conference, 12:30 to 2:00 p.m.
Meeting, 2:00 to 4:00 p.m.

Summer Camps For Diabetic Children

*Alexander Marble, M.D.**

NEW ENGLAND DEACONESS HOSPITAL, BOSTON

Those interested in providing summer camp facilities for diabetic children have been encouraged by the establishment of various new camps throughout the country during the past few years. Others are in the planning stage. It seems appropriate, therefore, to summarize available camp information in the hope that this material may be useful to those who are considering the establishment of new camps or are in the process of starting them. In the preparation of this paper the writer has drawn freely from a thesis prepared by Miss Minette Katryn Shanahan in 1947 at the University of California, and entitled "Camping Provisions for Diabetic Children in the United States." Data have also been obtained from the 1948 report of Dr. Henry J. John, then Chairman of the Committee on Camps of the American Diabetes Association.[1] Finally, information has been obtained from questionnaires which were courteously answered by those in charge of the various camps. The writer's comments are based chiefly on observations at the two camps in Massachusetts and may not always reflect the views of others.

HISTORY

The idea of summer camps for diabetic children is not a new one. In 1925, only three years after the introduction of insulin into clinical usage, Dr. Leonard F. C. Wendt of Detroit started a small camp. In the beginning there were only four campers, who were housed in a private cottage owned by a diabetic patient. As the camp grew in subsequent seasons, it was held at various sites and under various auspices. The camp was closed during World War II. It reopened in 1946, but since then has again discontinued operations.

The second camp was established by Dr. Henry J. John of Cleveland in 1929, under the name of Camp Ho Mita Koda, a phrase from the language of the Sioux Indians which means "Welcome, my friend." This camp is located on 40 acres of wooded land near Newbury, Ohio, about 30 miles east of Cleveland. The camp was closed while Dr. John was in the Army in World War II, but it reopened for the 1947 season.[2, 3]

As early as 1927 Dr. Elliott P. Joslin and associates began sponsoring camping facilities for diabetic children. For several years the camps were small and were held under various auspices and in various places in Massachusetts, New Hampshire and Maine. In 1932 a permanent arrangement was made for girls at the Clara Barton Birthplace Camp, North Oxford, Massachusetts. In 1948 a permanent camp was established for boys in the adjoining town of Charlton, Massachusetts; it is called the Elliott P. Joslin Camp.[4, 5] These camps are administered by the Association of Universalist Women, which for years has donated much time, effort and money. Substantial financial support has also been given by the Massachusetts Committee on Social Service of Unitarian Women.

Another early camp was that sponsored by the Metabolic Clinic of the University of Pennsylvania Hospital. In 1935 small groups of diabetic children were cared for at the University Camps of the Christian

*Chairman, Committee on Camps, American Diabetes Association.

Association of the University of Pennsylvania. In 1936 Camp Firefly, the Pennsylvania Camp for Diabetic Children, was established by the Philadelphia Metabolic Association. Conducted under the auspices of the John B. Deaver Memorial Auxiliary of the Lankenau Hospital, it has used various sites but is now located at Spring Mount, Pennsylvania.

In 1937 the New York Diabetes Association opened a camp for diabetic children which has operated yearly since. The camp has grown and developed steadily. In 1945 a permanent site was purchased for Camp NYDA at Burlingham, N.Y. In 1951 the camp accommodated 171 children.

Also established in 1937 was the Washington Camp for Diabetic Children at Rockville, Md. Medical sponsorship comes from physicians in Washington, D. C.

The establishment of camps has by no means been confined to the eastern part of the country. As early as 1938 Camp Banting and Camp Priscilla White were established in the state of Washington, and in the same year Camp Whitaker was opened in California. University Camp, also in California, was opened in 1941 for one season, closed for the war period, and reopened in 1946.

The number of camps has now grown to 18, including one in Canada. This is Illahee Lodge at Cobourg, Ontario. It is owned and operated by the Neighborhood Workers Association, and sponsored by the Kinsmen Clubs, both of Toronto. It is not run solely for diabetics, but is operated also for children with other medical conditions. Of the 50 children who can be accomodated at each of three camp sessions there are, on the average, about 15 diabetics.

DATA REGARDING CAMPS NOW IN OPERATION

Information regarding the 18 camps has been summarized in Table 1. It is evident that although the camps are scattered quite well over the country, there are certain large areas of the United States and Canada in which a diabetic child would need to go hundreds of miles to a summer camp. The need for new camps in these areas is obvious.

Taking into account the increased capacity of those camps which have more than one session, the number of children which can be accommodated in all camps is 1996. During the summer of 1951 a total of 1304 children actually attended. This lower figure was due in part to the fact that, in camps having more than one session, certain campers stayed for more than one period. However, the figures do indicate that, in addition to the need for additional camps in certain areas now unserved, the facilities of some of those camps already established could be used more completely. Physicians caring for diabetic children should urge them to seek the benefits of a summer camp stay.

The rates quoted in Table 1. cannot in most instances be regarded in the same way as listings for private camps. In most camps the money received is more in the nature of a contribution, since the camps are nonprofit organizations usually dependent upon public support of one type or another. Furthermore, the rates listed in the table cannot be compared from one camp to another, since each camp, to the full extent of its resources, accommodates children regardless of ability to pay. The matter of the cost of camp operation is discussed later in the paper.

ESTABLISHMENT AND OPERATION OF A SUMMER CAMP

Sponsorship

The operation of a summer camp for diabetic children can never be a money-making venture. To accommodate the children who most need the benefit of a camp stay, the cost must be subsidized in large part. Fortunately for this purpose, the health and welfare of children have a strong public appeal. Prior to the organization of the American Diabetes Association and its Affiliates, camps were established by physicians or groups of physicians who often secured the support and cooperation of church organizations, civic clubs, nonmedical professional societies, business associations with charitable programs, and similar groups. In view of the increasing interest in the formation and development of Affiliate Associations, it is likely that in the future the sponsorship, organization and financing of new camps will become an important and extremely worthwhile activity of these Affiliates. Financial support can be found among the groups mentioned above. Physicians interested in and responsible for the medical aspects of summer camp work can usually help most by concentrating on professional activities among the children. Consequently it is often better if the operation and administration of the camp is the responsibility of the lay organization which has helped to organize and finance the camp, such as the Lay Society of an Affiliate.

Site

Ideally a camp should be located in a wooded area and include, or have access to, a pond, lake or stream for

water sports. Facilities for walks in the woods, nature study, "cook-outs" and overnight camping add a great deal to the pleasure and benefit derived by the diabetic child. However, almost any camp site is acceptable provided the sponsors of the camp offer a carefully planned and executed program. Land and buildings may be owned by the sponsoring group, trust or foundation. However, if this is found to be too costly an enterprise, often an arrangement may be made to rent part or all of a camp already established, such as a Boy or Girl Scout Camp, a civic or church camp or retreat, etc., for a few weeks of each summer.

Length of Camp Season

In establishing a new camp it is wise to start modestly, providing at first for single sessions of 2 or 3 weeks, with perhaps one session for boys and one for girls or a combined session if only younger children are to be accommodated. Local needs, estimates of attendance, and availabilty of facilities must govern the decision in this regard. If at all possible, the camp session should last at least 2 weeks to provide maximal benefit both from a recreational and medical standpoint. If the number of prospective applicants and facilities allow, arrangements may be made for 2 to 4 sessions of 2 or more weeks each.

Age of Campers

Children from 5 or 6 up to 15 or 16 years of age may be handled successfully. Those less than 5 years old present a problem in individual care, and even for children who are 5 and 6 years old, arrangements for special supervision will be necessary. Those in the highest age groups may become "counsellors-in-training."

Organization

In smaller camps with perhaps only one session of 2 weeks, the organization may well be informal, with most if not all workers on a voluntary basis. However, in larger camps the organization must be made quite business-like and the whole affair will necessitate much careful planning year after year. The basic structure resembles that of the privately operated summer camp, but the organization is made more complex by the need for a medical as well as a recreational staff. The Camp Director is aided by a Program Director and by counsellors especially chosen for their experience and skill in directing various camp activities. Among the more important of these are swimming; land sports including baseball, volleyball, track and archery; and nature study, music and dramatics. It is desirable to have one counsellor for each four campers. The medical staff should include a Resident Physician, nurses, dietitian and laboratory technicians. There must be close cooperation between recreational and medical staffs.

Program

In a camp for diabetic children it is essential that the Camp Director and the Resident Physician work together closely so that the program may allow time for necessary events of a medical nature. Insulin must be given at a definite time, meals and between-meal lunches must be served regularly and a certain minimum of laboratory tests must be carried out. Some thought in scheduling times of physical activity and of quiet periods will do much to lower the incidence of insulin reactions.

Despite these limitations, it is entirely possible to arrange a full and varied program of sports, nature study, music and dramatics which will both please and develop the diabetic child. The program in certain camps is discussed in papers already published.[2-8]

Buildings

It would not be profitable here to discuss the number and type of buildings necessary and desirable since use must be made of what is available or what can be afforded. Ideally the structures should include cabins for housing small groups of campers and their counsellors, a dining hall and kitchen, a recreation hall, an administration building, an infirmary, a laboratory, and staff quarters. The infirmary should provide one or more beds for campers with minor ailments. The laboratory should provide facilities for the determinations of sugar in urine and blood, for general urine analyses, and such other tests as are contemplated. For descriptions of the physical plant of certain camps, the articles by John,[2] Gabriele and Marble,[4] Grishaw[6] and Sweeney[8] should be consulted.

Cost

In the present day it is costly to run a summer camp of any type. When one adds to the recreational features the medical provisions cited above, the expense is increased considerably. One must pay acceptable salaries for a Camp Director, for counsellors, for nurses, dietitians and laboratory technicians if one is to attract well-qualified workers. At the Clara Barton Birthplace Camp the cost in 1951 was $45 per girl per week. At the neighboring Elliott P. Joslin Camp the correspond-

Table 1. CAMPS FOR DIABETIC CHILDREN IN THE UNITED STATES AND CANADA

NO.	NAME	STATE OR PROVINCE	LOCATION	OWNER OR SPONSOR	DATE FOUNDED	TERM
1.	Seale Harris Camp	Ala.	Citronelle near Mobile, Ala.	Diabetic Clinic of Mobile, Inc.	1949	2 weeks
2.	University Camp	Cal.	San Bernardino Mountains above Redlands, Cal.	Los Angeles Metabolic Clinic	1941	2 weeks
3.	Camp Whitaker	Cal.	Near King's Canyon National Park	Diabetic Youth Foundation	1938	Two 2-week periods
4.	Washington Camp for Diabetic Children	Md.	Rockville, Md.	Christ Child Farm for Convalescent Children	1937	One month
5.	Clara Barton Birthplace Camp	Mass.	North Oxford, Mass.	Association of Universalist Women and The Diabetic Fund	1931	Five 2-week periods
6.	Elliott P. Joslin Camp	Mass.	Charlton, Mass.	Association of Universalist Women and The Diabetic Fund	1948	Three 3-week periods
7.	Camp Friendly	Mich.	Lake Olcott, Napoleon, Mich.	Toledo Diabetes League	1950	2 weeks
8.	Camp Lake of the Woods	Mo.	Swope Park, Kansas City, Mo.	City and Lay Diabetic Society of Kansas City	1951	2 weeks
9.	Springdale Camp	Nebr.	Nebraska City, Nebraska	Springdale Camp Corp.	1951	2 weeks
10.	Camp NYDA	N. Y.	Burlingham, New York	New York Diabetes Association, Inc.	1937	Three 3-week periods
11.	Camp Ho Mita Koda	Ohio	Newburg, Ohio	Board of Trustees of Camp	1929	Two 1-month periods
12.	Illahee Lodge	Ontario	Cobourg, Ontario	Neighborhood Workers Association and Kinsman Clubs of Toronto	1946	Three 3-week periods
13.	Camp Firefly	Penna.	Spring Mountain, Penna.	Philadelphia Metabolic Association	1935	Boys: 3 weeks Girls: 3 weeks
14.	Sweeney Camp for Diabetic Children	Texas	Gainesville, Texas	Sweeney Diabetic Foundation	1950	Three 4-week periods; also 2-week
15.	Camp Banting	Wash.	Seattle, Wash.	Diabetic Trust Fund, Virginia Mason Hospital	1938	2 weeks
16.	Camp Priscilla White	Wash.	Seattle, Wash.	Diabetic Trust Fund, Virginia Mason Hospital	1938	2 weeks
17.	Camp Kno-Koma	West Va.	Near Charleston, West Va.	West Va. Diabetes Association; Carbide and Chemical Corp.	1950	9 days
18.	Holiday Home Camp	Wisc.	Lake Geneva, Wisc.	Chicago Diabetes Association	1949	3 weeks

CAPACITY AT ANY ONE TIME			CHILDREN ACCOMMODATED 1951			AGES YEARS	RATES*	RESIDENT PHYSICIANS	NURSES	DIETITIANS	CONTACTS
Boys	Girls	Total	Boys	Girls	Total						
30	30	60	14	16	30	8-14	$40 for 2 weeks	1	2	1 full time 1 part time	Miss Jeannette Overstreet 815 Van Antwerp Building Mobile, Ala.
		75	34	33	67	8-16	$65 for 2 weeks	2	1	1	Los Angeles Metabolic Clinic 1930 Wilshire Blvd. Los Angeles 5, Cal.
50	50	100	64	66	130	6-16	$40 for 2 weeks plus travel	1	1	4	Mary B. Olney, M.D. 1429 4th Avenue San Francisco 22, Cal.
		10	4	5	9	6-12	$4 daily	0	3	1	K. Hammond Mish, M.D. 1726 Eye St., N. W. Washington 6, D. C.
0	55	55	0	170	170	5-15	$45 per week	1	3	0	Priscilla White, M.D. 81 Bay State Road Boston 15, Mass.
56	0	56	135	0	135	5-16	$50 per week	1	3	1	Alexander Marble, M.D. 81 Bay State Road Boston 15, Mass.
		40	6	12	18	—	$5-$10 weekly	1 or more	2	1 or 2	Miss Eleanor Peterson Toledo Diabetes League Acad. of Med. Bldg., Toledo, O.
50	50	100	11	9	20	8-16	$35 for 2 weeks	1	1	2	Harry M. Gilkey, M.D. 1103 Grand Avenue Kansas City, Mo.
12	24	36	8	12	20	9-16	$50 for 2 weeks	1	1	1	Miss Anna Smrha Dept. of Health State Capitol Bldg., Lincoln, Nebr.
40	40	80	83	88	171	6-16	Cost per week: $75 - $80	1	4	2	Thomas H. McGavack, M.D. New York Diabetes Assn. 2 E. 103rd St., N. Y. 29, N. Y.
30	30	60	39	34	73	6-16	$175 per month	1	2	2	Mr. Rex W. Thornburgh R.F.D. 2 Chardon, O.
app. 15	app. 15	app. 30	26	18	44	5-16	$128 for 3 weeks	1	1	2	Miss M. Collver 22 Wellesley Street Toronto, Can.
30	32	62	30	32	62	6-15	Up to $5 a day	1	1	1	Miss Clara Woodward 1530 Spruce Street Philadelphia 2, Pa.
44	44	88	114	112	226	6-18	$300 for 6 weeks	2	3	2	J. Shirley Sweeney, M.D. Gainesville, Tex.
18		18	7		7	10-14	$28 for 2 weeks	0	1	1	Lester J. Palmer, M.D. 1115 Terry Avenue Seattle, Wash.
	18	18		10	10	10-14	$30.50 for 2 weeks	0	1	0	Lester J. Palmer, M.D. 1115 Terry Avenue Seattle, Wash.
70	70	140	22	23	45	7-15	No charge	1	3	2	George P. Heffner, M.D. West Va. Diabetes Assn. 1115 Quarrier St., Charleston, W.Va.
40	40	80	33	34	67	8-14	$120 for 3 weeks	1	2	2 or 3	Chicago Diabetes Assn. 110 South Dearborn Street Chicago, Ill.

* In most instances the stated rates are not absolute but are given only as a guide. The usual statement is that no child will be refused admission because of lack of ability to pay.

ing figure was $50 per boy per week. These are minimum figures, since both camps are operated as nonprofit undertakings with no charge whatever for the services of sponsoring physicians. It is obvious that relatively few parents of diabetic children are able or willing to pay this much for two or more weeks each summer. Consequently the policy in these two camps has been to make no set charge but to ask the parent to contribute as much as he can up to the actual cost. Experience over years of time has shown that approximately 40 per cent of the cost of the camp will be cared for by such contributions by parents. The rest must be made up by funds obtained by appeal to the public, to diabetic patients, to church and civic organizations and other sources. *One must be in a position to state that no child will be turned away because of lack of finances.* On the other hand, an arrangement in which almost everyone contributes something, even though a small sum, creates self-respect, increased interest, and better appreciation of the privilege of going to camp.

OBJECTIVES OF THE SUMMER CAMP PROGRAM

Among those interested in summer camps for diabetic children there are two viewpoints as to the prime objective. One group takes the stand that the recreational aspects are most important and that medical matters should be relegated to the background. According to this view, urine and blood testing should be kept to a minimum and the children be allowed to enjoy camp life. Those of opposite mind believe that the summer camp affords an unparalleled opportunity for a "check-up" with regulation of the diabetic condition, and for the education of the child regarding home care.

Actually these two viewpoints conflict very little and can easily be reconciled. One aim of a camp should be to provide for the diabetic child an enjoyable vacation such as his nondiabetic brothers and sisters have, with a chance to camp out, to learn to swim, to engage in land and water sports and to experience the pleasures of group living. The other aim, entirely compatible with the first, should be to work out an adequate yet restricted diet; to arrive at a workable insulin schedule; and to teach by example and by informal discussions the meaning of good control of diabetes, the means of attaining it, and the necessity for it if complications are to be avoided. This means that medical attendants in an unobtrusive way arrange for diet, insulin and laboratory tests in a fashion not unlike that provided in well-run hospitals accustomed to caring for diabetic patients.

In a summer camp the diabetic child who may have felt "different" and lonely while at home with nondiabetic companions is comforted by association with others whose condition is the same as his. He develops a satisfying group spirit. He gains confidence and becomes more self-reliant. These psychological advantages are great. In this connection it is well to emphasize the need for further understanding of the psychological problems of the diabetic child and adolescent so that one may be in a better position to cope with them. The summer camp provides an unparalleled opportunity for such a study.

An advantage of summer camps that must not be overlooked is the rest and freedom from worry afforded the parents during the period of the camp session.

THE FUTURE OF CAMPS FOR DIABETICS

Those who have had experience with camps for diabetic children agree that they are extremely worth while. Any time and money invested in them will yield extraordinarily high returns in health, happiness and character-building. Furthermore, they provide a means of diabetes regulation for children who otherwise would lack detailed supervision in these days of high hospital costs. As previously stated, money should not be a barrier preventing a child from benefiting from camp experience. Not only are additional camps needed to take care of certain sections of the country now lacking facilities, but those camps already in operation must use all possible means to encourage attendance by diabetic children in the area served. Estimates vary widely as to the number of children under 16 who have diabetes in this country, but whether the number is 15,000 or 50,000 (to quote different estimates) it is obvious that extension of camp privileges to more children is needed.

One other development of the summer camp program deserves mention, and that is the extension of the medical and recreational benefits to older diabetic patients. For the last few years at the Clara Barton Birthplace Camp, the fifth session of two weeks at the close of summer has provided camp experience for older girls and young women. A similar program will be attempted this summer at the Elliott P. Joslin Camp for one week following the close of the regular camp season. Such plans, if proven feasible and of definite value to the older camper, would provide greater usage of the physical facilities of the camp.

The development of camps for diabetics, particularly those in younger age groups, is closely related to the

future of the diabetics themselves. Evidence is accumulating to indicate that the late vascular complications of diabetes are related not only to the duration of the disease but also to the degree of its control over the years. Although there is not as yet unanimity of opinion in this regard, the writer believes that only by careful, continuous control can these complications, as well as the late neuropathies, be prevented or delayed. A yearly stay at a well-run summer camp will contribute much to the regulation, education and development of diabetic children, and will help them to live longer, healthier and happier lives.

SUMMARY

1. Data are presented regarding the 18 summer camps for diabetic children in the United States and Canada. Suggestions are given regarding the establishment and operation of camps.

2. With a capacity of about 2000, camps in 1951 accommodated about 1300 children. The need for additional camps in unserved areas as well as for greater usage of established camps, is stressed.

3. The objectives and future of the summer camp program are discussed.

REFERENCES

1 John, H. J.: Report of the Committee on Camps. Survey of camps for diabetic children in the U. S. Proc. Amer. Diabetes A. *3*:321-26, 1948.

2 John, H. J.: The planning of a camp for diabetic children. Am. J. Med. *1*:642-48, December 1946.

3 McCullagh, E. P., Russell, P. W., and Schneckloth, R. E.: A summer camp for diabetic children. Ohio State M. J. *46*:452-54, May 1950.

4 Gabriele, A. J., and Marble, A.: Experiences with 116 juvenile campers in a new summer camp for diabetic boys. Am. J. M. Sc. *218*:161-71, August 1949.

5 Stephens, J. W., and Marble, A.: Place and value of summer camps in management of juvenile diabetes. Am. J. Dis. Child. *82*:259-67, September 1951.

6 Grishaw, W. H.: Diabetes camp. A.D.A. Forecast, July 1948.

7 Heffner, G. P., and Miller, A. P.: West Virginia's first camp for diabetic children (a report on Camp Kno-Koma). West Virginia M. J. *47*, January 1951.

8 Sweeney, J. S.: The South's first full summer camp for diabetic children and observations on the use of NPH insulin. South M. J. *44*:1157, December 1951.

The Committee on Scientific Exhibits

REPORT TO THE COUNCIL OF THE AMERICAN DIABETES ASSOCIATION, 1951-1952 INTERIM MEETING JANUARY 19, 1952

The Committee held its first meeting for this year on January 6, 1952. Four of the six members were present, including one ex-officio member, and it is felt that much that was useful was accomplished.

Two major subjects were considered. The first was the preparation of an exhibit for scientific meetings and other professional audiences, and the second was the development of a lay exhibit. The latter project had earlier been assigned to the Subcommittees on Scientific Exhibits and on Health Information, neither of which now exist. The scientific exhibit was discussed because it was thought desirable to develop something new for the 1952 Annual Session of the American Medical Association.

THE SCIENTIFIC EXHIBIT

The Committee decided that an exhibit entitled "Vascular Complications of Diabetes" would be both instructive and timely, and suggested a five-panel display to fit a booth built to American Medical Association specifications and consisting of a 12-foot back wall and two

6-foot side walls. Three panels would be placed on the back wall and one on each side wall.

The Committee proposed that the center panel on the back wall should consist of a nondetailed sketch of a human being. The panel to the right would show four x-rays which would depict by injection circulation sclerosis. The left hand panel on the rear wall would display seven photographs: a normal eye, an eye with retinitis, and an eye with retinitis proliferans; the normal kidney and a kidney showing the Kimmelstiel-Wilson syndrome; and a foot with gangrene and one with an ulcer.

The left and right side panels would consist of type display, and would read approximately as follows:

Left Panel. POSSIBLE CAUSATIVE FACTORS OF VASCULAR DISEASE IN DIABETES: 1, Duration of disease; 2, inadequate control; 3, disturbances in cholesterol and lipid metabolism; and 4, constitutional predisposition. SPECIFIC FACTORS COMPLICATING VASCULAR DISEASE IN DIABETES: 1, Severe frequent hypoglycemia, increasing the work of the heart and causing thrombosis; 2, trauma—chemical, thermal or physical; and 3, infection.

Right Panel. METHODS OF AVOIDING VASCULAR COMPLICATIONS IN DIABETES: 1, Adequate control of the diabetes; 2, avoidance of obesity; 3, avoidance of known complicating factors; 4, attempt to improve circulation by (a) sympathectomy and (b) vasodilators such as drugs, alcohol, mechanical; 5, prompt treatment of infections by appropriate measures, including chemotherapy and antibiotics; and 6, early surgical consultation in infection and gangrene.

THE LAY EXHIBIT

The Committee proposed that this exhibit could consist of a series of four pictures of human beings, each one graphically depicting food intake, insulin production, and blood sugar levels. The first drawing would be that of a nondiabetic—that is, a person in balance. The second would show a noncontrolled diabetic; the third a mild diabetic in whom control is established by diet alone; the fourth a severe diabetic who requires insulin injections as well as diet restrictions in order to maintain control.

The exhibit would also answer, by text, some of the basic questions that arise in people's minds: What is diabetes? Who gets diabetes? What are the symptoms of diabetes? and so forth.

RECOMMENDATIONS*

The Committee recommended that the American Diabetes Association prepare a new scientific exhibit entitled "Vascular Complications of Diabetes" for the 1952 American Medical Association Annual Meeting, and that the sum of $1,000 be appropriated for the construction of such an exhibit.

It further recommended that a lay exhibit be prepared, that its title should be "What is Diabetes?" and that an appropriation of $500 (in addition to a previous allocation of $500) should be made for the construction of this exhibit. In view of the fact that the suggested lay exhibit is for the general public, it was suggested that the Committee on Scientific Exhibits be authorized to work with the Committee on Detection and Education, which has taken on some of the functions of the former Subcommittee on Health Information, in the development and preparation of this exhibit.

JULIAN D. BOYD
W. WALLACE DYER
WILLIAM S. REVENO
DONALD S. SEARLE
J. ROSS VEAL
HENRY B. MULHOLLAND, *Chairman*

* The recommendations proposed in this Report were approved by the Council of the American Diabetes Association at its Interim Meeting, January 19, 1952. — Ed.

ASSOCIATION NEWS

TWELFTH ANNUAL MEETING

The program for the Twelfth Annual Meeting will be found on pages 242-244 of this issue. The Scientific Sessions have been expanded to include three panel discussions running concurrently; these have been patterned after those successfully conducted by The American College of Physicians. Also included is a Conference of Affiliate Associations. Not all of the increased activity at the Annual Meeting is indicated in the program, however, as the following Committee, Council, and Board meetings are scheduled:

Wednesday, June 4
1:30 p.m., Executive Committee

Thursday, June 5
10:00 a.m., Committee on Constitution
2:00 p.m., Committee on Affiliate Associations
6:00 p.m., Committee on Scientific Publications

Friday, June 6
9:00 a.m., Committee on Finance
10:00 a.m., Committee on Membership
11:00 a.m., Committee on Emergency Medical Care
12:30 p.m., Council

Saturday, June 7
9:00 a.m., Council
12:00 noon, Committee on Scientific Exhibits
12:00 noon, Committee on Food Values

Sunday, June 8
8:00 a.m., Committee on Camps

Monday, June 9
8:00 a.m., Editorial Board, DIABETES
10:00 a.m., Committee on Detection & Education
11:00 a.m., Conference of Chairmen of Committees on Diabetes of County and State Medical Societies and Chairmen of Committees on Diabetes Detection of Affiliate Associations, sponsored by the National Committee on Detection and Education.

AMERICAN MEDICAL ASSOCIATION ANNUAL SESSION JUNE 9-13, CHICAGO

The program for the forthcoming American Medical Association meeting promises a number of sessions on diabetes. There will be an Exhibit Symposium on Diabetes, with Question and Answer Conferences; among the exhibits shown will be the American Diabetes Association's own new one, "Vascular Complications of Diabetes," which is described in the *Report* of the Committee on Scientific Exhibits, page 251 of this issue.

Other exhibits to be shown are:

LOOK FOR DIABETES. YOU WILL FIND IT—Hugh L. C. Wilkerson, Diabetes Section and Malcolm J. Ford, Program Development Branch, U.S. Public Health Service, Washington, D.C.

RURAL DIABETIC DETECTION—Wayne Griffith and Robert L. Richards, Chester, Vt.

CLINICAL AND PATHOLOGICAL STUDY OF DIABETIC RETINOPATHY—Jonas S. Friedenwald and Bernard Becker, Johns Hopkins Hospital, Baltimore, and A. E. Maumanee, Stanford University School of Medicine, San Francisco.

TREATMENT OF DIABETES MELLITUS—Howard F. Root, Elliott P. Joslin, Priscilla White, Alexander Marble, Allen Joslin, Robert Bradley, and Clifford C. Franseen, Boston.

MODIFICATION OF A NEW RAPID BLOOD SUGAR METHOD—E. A. Haunz and M. H. Reisdorf, Grand Forks Clinic, Grand Forks, N.D.

The Question and Answer Conferences, under the chairmanship of Dr. Howard F. Root of Boston, will run continuously as follows:

Monday, June 9 —10 a.m. to 4 p.m.
Tuesday, June 10 —10 a.m. to 4 p.m.
Wednesday, June 11—10 a.m. to 4 p.m.

Thursday, June 12 —10 a.m. to 5 p.m.
Friday, June 13 —10 a.m. to 12 noon

On Thursday, June 12, at 9 a.m., the Section on Internal Medicine will sponsor jointly with the Section on Experimental Medicine and Therapeutics a Symposium on Recent Advances in Diabetes Mellitus, as follows:

PATHOGENESIS—DeWitt Stetten, Jr., New York
Discussors: Rachmiel Levine, Chicago; Konrad Bloch, Chicago

OCULAR CHANGES—Jonas S. Friedenwald, Baltimore
Discussors: Paul Kimmelstiel, Charlotte, N.C.; Francis H. Adler, Philadelphia; George W. Dana, Baltimore

DEGENERATIVE VASCULAR COMPLICATIONS—Alexander Marble, Boston
Discussors: Lester J. Palmer, Seattle; James W. Sherrill, LaJolla, Calif.

MODERN TREATMENT—Henry T. Ricketts, Chicago
Discussors: Carlos P. Lamar, Miami; Blair Holcomb, Portland, Ore.

DIABETIC COMA—Randall G. Sprague, Rochester, Minn.
Discussors: Henry B. Mulholland, Charlottesville, Va.; James A. Greene, Houston

THE IMPROVED OUTLOOK OF THE DIABETIC PATIENT —Edwin L. Rippy, Dallas
Discussors: Russell M. Wilder, Bethesda, Md.; Leon S. Smelo, Birmingham

For the first time the American Diabetes Association will display its publications at the Technical Exposition of the A.M.A. meeting and members are cordially invited to visit Booth D-136 (please see page A-5 of this issue).

ADDITIONAL INFORMATION—FIRST CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The International Diabetes Federation's First Congress, to be held July 7-12 in Leyden, The Netherlands, was announced in the previous issue. According to information just received the Congress will have two purposes: 1, scientific meetings, and 2, conferences of representatives and delegates of the various international diabetes associations. Scientific lectures will be held during the daytime, while the conferences of representatives and delegates are scheduled for the evenings of Wednesday and Thursday, July 9 and 10. Excursions have been planned for every day in the week for those accompanying Congress registrants. An official program is scheduled for distribution the latter part of May.

NATIONAL HEALTH COUNCIL

The Thirty-Second Annual Meeting of the National Health Council, of which the American Diabetes Association is an active member, was held March 13-14 at the Hotel Roosevelt in New York City. Dr. Howard F. Root, member of the Board of Directors of the Council, attended the meetings, as did Dr. Joseph T. Beardwood, Jr. and J. Richard Connelly, Association delegates to the Council.

PERSONAL

Dr. Norman Jolliffe, Director of the Bureau of Nutrition of the New York City Department of Health, was named President of the National Vitamin Foundation, Inc. at the Foundation's annual meeting on April 3 in New York City. Dr. Jolliffe serves on the Association's Committees on Information for Diabetics and on Food Values. He also serves as a member of the Food and Nutrition Board of the National Research Council.

DIABETES ABSTRACTS

Last month a request was made for back copies of Vol. I of the *Proceedings* of the American Diabetes Association, dated 1941, and several copies have been received. Certain issues of *Diabetes Abstracts* are also out of stock and if anyone has duplicates or no longer has use for his own copies, it would be greatly appreciated if he would send them to the National Office. The following issues are completely out of stock: Vol. IV, Nos. 2 and 3; Vol. VI, Nos. 2 and 4; Vol. VIII, Nos. 1 and 2.

EMPLOYMENT FOR DIABETICS

The Medical Division of the United States Civil Service Commission has just issued a bulletin entitled "Positions in the Federal Civil Service for which Diabetics May Be Considered." The list, which contains approximately 1200 positions for which diabetics are eligible, is not available for quantity distribution and, therefore, it will be published in condensed form in the July-August 1952 issue of the *A.D.A. Forecast.*

THE HISTOCHEMICAL SOCIETY

An announcement of the formation of The Histochemical Society has recently been received. The Society will serve the new interest in histochemistry, its applications and methodologies. The Society will have its own publication, *The Journal of Histochemistry.* Information about the publication, as well as about membership in the

Society, may be secured from the Editor in Chief, R. D. Lillie, National Institutes of Health, Bethesda, Md.

OBITUARIES

REUBEN DAVIS, M.D., who joined the American Diabetes Association on March 18, 1941, died in Philadelphia on December 24, 1951, at 47 years of age. Dr. Davis was born in Jackson, Tennessee, and obtained his medical degree from Jefferson Medical College, Philadelphia, in 1929. At the time of his death he was Assistant Professor of Medicine at Temple University School of Medicine and Chief of the Metabolic Clinic in Temple University Hospital.

Dr. Davis was a member of the American Medical Association, The Endocrine Society, and the Philadelphia Metabolic Association, as well as the American Diabetes Association.

EDWARD PAUL LEEPER, M.D., of Dallas, Texas, member of the American Diabetes Association since February 1941, died on February 9 at the age of 48. Born in 1903 at Denison, Texas, Dr. Leeper was graduated from the University of Texas School of Medicine in 1928, and thereafter joined the faculty of Baylor University College of Medicine, as Assistant Professor of Clinical Medicine. Later he became Clinical Assistant Professor of Medicine at the Southwestern Medical School of the University of Texas.

Dr. Leeper was, in addition to being a member of the American Diabetes Association, a fellow of the American College of Physicians and the American Medical Association, and a member of the American Heart Association. He was affiliated with Parkland, Methodist and Medical Arts Hospitals, and served as Medical Director for the Praetorian Life Insurance Company.

A TRIBUTE TO OTTO MEYERHOF: 1884-1951

With the death of Otto Meyerhof on October 6, 1951, the world lost one of the most outstanding scientists of this century. The revolutionary character of his thinking, the originality of his approach, and the brilliance of his experimental work had a profound influence upon the progress of physiology and biochemistry—indeed, upon the progress of biology as a whole, and consequently upon the medical research of the past few decades. . . . . .

Meyerhof demonstrated that muscle glycogen is the precursor of the lactic acid formed in the absence of oxygen. He further showed that, in the presence of oxygen, some of the lactic acid formed during the anaerobic contraction was oxidized, but that not all the lactic acid underwent this fate. About one fifth to one fourth of it was oxidized to carbon dioxide and water, and the energy of this oxidation was used to reconvert the remaining four fifths or three fourths to glycogen. His discovery thus confirmed and extended Pasteur's hypothesis that fermentation (or glycolysis) is "la vie sans air" *in that, to a certain extent, it substitutes for respiration. His observations actually proved Pasteur's assumption that less carbohydrate is consumed in the presence of oxygen than in its absence. The depression of glycolysis by respiration has since been referred to as the Pasteur-Meyerhof effect. Meyerhof's brilliant analysis of the glycogen-lactic acid cycle and its relation to respiration explained the course of the heat production and, for the first time, established the cyclic character of energy transformations in the living cell. For this accomplishment Meyerhof received the Nobel prize in physiology and medicine in 1923 (when he was only 39 years old), together with his colleague and friend A. V. Hill. . . . .*

The impact of Meyerhof's personality and of his work is perhaps best illustrated by the great number of scientists who received inspiration and training in his laboratory. . . . . The combination of a great scientist and a great man made him a real leader and one of the most distinguished representatives of modern science.

—From a memorial essay by David Nachmansohn,
Severo Ochoa, and Fritz A. Lipmann, *Science*, April 4, 1952.

A.D.A. *Forecast*

There are FOUR basic components in the treatment of your well-controlled diabetic patients. They are: diet—insulin—exercise—*and* the A.D.A. FORECAST, the American Diabetes Association's own magazine for lay diabetics. The FORECAST, which comes out every other month, is edited by Frederick W. Williams, M.D. If you are not already using it as a part of your patients' regimen, send in a subscription for your reception room, or a request for subscription blanks for your patients or both. Or if you would rather see what it is like first, a postcard will bring you a sample copy.

Subscription rates: 1 year, $2.00; 2 years, $3.50; 3 years, $4.75. Add 25c per year for subscriptions outside the U.S. and Canada.

Subscription Department, A.D.A. FORECAST
American Diabetes Association, Inc.,
11 West 42nd Street, New York 36, N. Y.

NEWPORT PRESS, QUEENS, N.Y.